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THE
OUNT SINAI JOURNAL
F MEDICINE

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Issues in Medical Ethics

1. The Doctor-Patient Relationship
2. Transplantation: Ethics and Organ Procurement

Daniel A. Moros and Rosamond Rhodes, guest editors

From the Mount Sinai School of Medicine (CUNY)

plus

David Z. Starr on a doctor's experience as a hospital patient

Kenneth I. Shine on science and responsibility

Faye Wattleton on the political responsibility of doctors

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THE MOUNT SINAI JOURNAL OF MEDICINE

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Issues in Medical Ethics

Introduction

Daniel A. Moros
Rosamond Rhodes

CONCERNS about our ability as a society to fairly and intelligently distribute the increasingly expensive fruits of our technology, and concerns about patient rights, patient autonomy, physician duties, and the limits of medical paternalism have acquired increased prominence as this century enters its final decade. Our ability to intervene in human disease leads us to invade both body and psyche in ways that earlier in this century would have seemed science fiction. Yet the relationship of physician and patient requires further understanding and explicit definition. In an earlier era, when medicine offered little, the ethical issues embedded in medical care, while interesting, only occasionally received serious attention. But medical care and the health care budget can no longer be treated casually. The need for individuals from many disciplines—philosophy, law, government, as well as physicians—to meet and discuss such issues is now well appreciated. This was not so clearly the case in 1986, when the first in what has become a yearly New York Regional Conference in Medical Ethics was held at Mount Sinai Medical Center.

This issue of the *Journal* presents the proceedings of the 1991 and 1992 conferences sponsored by The Mount Sinai School of Medicine and The Ph.D. Program in Philosophy of The Graduate School, CUNY. The proceedings of the 1987–1990 conferences have been published in two earlier special issues of *The Mount Sinai Journal of Medicine*. At the 1991 and 1992 conferences, practicing physicians presented selected cases to challenge the philosophical perspectives offered by the primary speakers. Each session ended with a panel discussion between all participants.

The Doctor-Patient Relationship: Whose Contract Is It? Our view of the proper conduct of the physician-patient relationship has changed dramatically over the past three decades and reflects our society's efforts to recognize individuals' rights for self-determination and to empower individuals to exercise their rights. This change is most evident in the demand for informed consent and the expectation that doctors will seriously try to understand the patient's objectives rather than simply paternalistically direct and dictate the course of medical care.

But the doctor-patient relationship also has meaning for the physician. It is not simply that the physician is entitled to earn a living practicing medicine. Many physicians have chosen medicine as a way of life and are deeply concerned with acting forcefully and correctly. At the 1991 conference, philosophers Bernard Baumrin, John Ladd, Laurence McCullough, and W. D. White and physician Daniel A. Moros presented their views on the nature of the doctor-patient relationship. Four young physicians, Alisan Goldfarb, Tom Kalb, Bennett P. Leifer, and Audrey Schwersenz, then presented cases from their practices which have raised doubts about what the patient-physician relationship would require of them.

For a panel discussion they were joined by Dr. Arthur H. Aufses, Jr., chairman of Mount Sinai's Department of Surgery, Dr. Richard Gorlin, chairman of Mount Sinai's Department of Medicine, and Mount Sinai Director of Patient Representatives Ruth

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Ravich. Among the issues considered in the 1991 conference are:

- Can this relationship be considered a straightforward commercial contract for service?
- What are the duties of a physician?
- Does the patient have any duties in the relationship?
- Are there special virtues that characterize the good physician?
- Can the good physician act from "legitimate self-interest"?

Transplantation: Ethics and Organ Procurement. The ethical issues raised by organ transplantation, where the recipient may be in desperate need of a limited resource, where the living donor may assume some risk, and where there may be opposition to the use of cadaveric and fetal tissue, illustrates how moral reasoning is challenged by our increasingly powerful ability to intervene in human illness. The transplantation issues are so various and complex that our 1992 conference focused entirely on the ethics of organ procurement.

Angelina Korsun began by explaining the organ procurement process. Philosophers Thomas Tomlinson and Rosamond Rhodes then presented their views on the acceptability of taking organs from questionable donors. Medical transplant specialists Steven Fruchtman, Harry Schanzer, and Myron E. Schwartz then described cases from their own experience with donors who did not fully have the capacity to consent. All these participants joined in a debate about the proper approach to the questionable donors whose cases had been presented.

Getting and giving organs was the second focus of the 1992 conference. Attorney Beth Essig explained the laws governing organ sales, and attorney Dena S. Davis and philosopher Gerald Dworkin addressed philosophical issues raised by the mechanics of getting organs. For discussion they were joined by physicians Robert M. Arnold from the Center for Medical Ethics at the University of Pittsburgh, Lewis Burrows, Mount Sinai's director of kidney transplantation, and Charles Miller, Mount Sinai's director of liver transplantation. Among the issues considered in the proceedings are:

- May infants and others who lack the capacity to consent be used as organ donors?
- Who cannot be a donor?
- Is it proper to sell organs?
- May a donor specify the recipient of a cadaveric organ?
- Should those who do not promise to give organs be eligible to receive them?

In this collection we again draw attention to serious issues which are urgently confronting the medical community. We remain committed to our goal of providing a multidisciplinary forum for wrestling with the emerging ethical issues which confront medicine, so that those from the ivory towers of academia and those from the trenches who have to make painful medical decisions can teach and learn from one another.

1. The Doctor-Patient Relationship

Whose Contract and What Is It?

The Doctor-Patient Agreement

BERNARD BAUMRIN, PH.D., J.D.

MOST CONTRACTS are implicit; some others are plain promises; only a few are written, and those are created mainly to involve the courts (and the police power the courts command) in enforcement. The courts, of course, will also enforce some oral promises, and they will enforce some implicit contracts. I want to focus my attention on implied contracts (and only derivatively on their enforcement) because I see the contracts that exist in medical care and service to be largely of this nature. I say "largely" because to the extent that they occur at all, oral promises and written agreements merely punctuate the periphery of the implicit core.

Implied Contracts. First, some examples of simple implicit contracts. I go to the supermarket; I pick up a can of tuna fish; I go to the checkout person, who rings up the price, and I hand her the money; she bags the tuna fish and I exit. All is well; but to illustrate the contractual character of this example, consider the sorts of things that could be amiss. I go to the store; they do not let me in, though they are open for business; I enter; there is no tuna fish for sale (they have it, but not for me, or only for special customers); there is tuna fish, it has no posted price, and the price is then fixed for me (in ways that I think nonstandard, too high, too low); I go to the checkout person, who rings up a different price; I go to the checkout counter and walk through without paying; I pay, she does not give me the tuna fish. All of these events are breaches of contract; all of them, in fact, are actionable in one way or the other, with enforceable remedies, including injunctions, damages. And that, of course, is not the end of it. The tuna fish may be contaminated; there may be less tuna in the can than as labeled; there may be no tuna in the can; the can of tuna may be part of a catch of stolen tuna. The list is not endless, but it is long.

A second example, having nothing to do with the simple purchase of anything: I stop at a shoeshine stand, I sit, I put my feet up, and my shoes are sandpapered, or changed from brown to black, or even just ignored. In both of these examples, no words need be spoken, yet it is perfectly clear that the contracts exist, and it is perfectly clear what sorts of thing would be a breach of the contract.

One of the deepest elements in contract law is the concept of reliance. We can generally agree that at least one party thought they had a contract if they can be perceived as having relied on (to their possible detriment) the behavior of the other. So, to the extent that one party's behavior tends to underlie a well-founded belief by the other party that the first will do this or that, and the believer acts as if he had the belief, the party whose behavior gave rise to that belief is bound contractually to satisfy the other's expectations. His failure to do so is an actionable breach of contract even if nothing has been said or written. Of course, if something has been either said or written, it will be easier to prove that the other's reliance was well-founded, but that is a mere matter of proof, not principle.

Estoppel. Along these lines, we have in law an evidentiary doctrine which forestalls someone from testifying that they did not do, or did not intend to do, or did not say, or did not write whatever the complainer (plaintiff) relied on. This is called an estoppel. In general, an estoppel operates when there is good evidence that someone did, or said, or wrote, something; he or she is es-

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Adapted from the author's presentation at the conference "Whose Contract Is It Anyway? Examining the Doctor-Patient Relationship" at the Mount Sinai Medical Center on March 8, 1991. From the Department of Philosophy, Lehman College and The Graduate School, CUNY. Address reprint requests to the author at 590 West End Avenue, New York, NY 10024.

topped from denying it (merely because it would now be helpful to do so). If the jury could form the belief that the plaintiff claims to have formed, the defendant will not be allowed to testify that he did not do it, say it, write it, or mean it. He never even gets to say the plaintiff is a fool, or gullible, or even just plain mistaken.

Physicians and Patients. The foregoing is a short version of a few elementary points about contract. Many other critical points will come up along the way. The person (we may in general look at persons as patients from here on) is a purchaser of services (like one who wishes his shoes shined or craves a can of tuna fish). The physician is an offeror. If this were all there was to it, then the patient purchases what he wants, the physician sells it, and that would be the end of the matter. It would not in principle differ from buying tuna fish or a shoe shine. But it is not the end of the matter, for several significant reasons. First, there is the "it": the patient wants health, or life, or recovery of function, or repairs. The larger the aim, the less likely it can easily be seen to be in stock. If we went to the market for nourishment, our quest would not be over because the shelves are stocked with edibles, and if we went to the shoe-shiner to look good, our shined shoes would be no guarantor of fulfillment of our search. Unshined shoes might not be our sartorial or cosmetic problem.

The State as Third-Party Guarantor. In coming to the physician, we go to one who is schooled in designing aid for many types of quests, though not all. He or she may have nothing for us, or there just may not be anything for us. So to begin with, the offeror (the doctor) is only offering a limited stock, which is generally speaking an implicit stock, so that the offeree (the patient) does not know exactly what is for sale or what he or she is getting. The patient may know that he is getting a private hearing and some other well-known aspects of the medical tradition, but of particular services he is largely ignorant. A partial solution to this problem is a state recognition of the offeror's expertise. The state licenses the offeror to sell an inchoate collection of wares, and further bars others from purporting to sell them. So into our doctor-patient relationship has stepped a third-party guarantor that has made itself a party to every such contract. The license the physician gets implicitly assures buyers of the wholesomeness of the goods.

The Doctoring Profession as Third-Party Guarantor. We are, however, not at an end here, for states are blind and notoriously ignorant. They like to make laws but not necessarily know any of the relevant facts. For this they turn to experts, and here they turn to physicians (who keep and have kept the arcane knowledge closely held) and say, "You tell us who to license and we will, but you had better not be mistaken or we will throw the business open to everybody." So the physicians' guild says, "O.K., we will tell you who, and we will do that by training them. So if we train them they count, and if we do not, they do not." That done, the whole profession (or at least those who train licensees) becomes another third-party guarantor of each physician-patient contract. By analogy, the profession assures quality control of the product, to which the state then grants an exclusive distributorship.

Now we can easily see that the patient approaches a twice-guaranteed purveyor who has been certified as an able selector and provider of the relevant product. The doctoring profession and the state have guaranteed that the patient can rely on the quality of the goods offered, on their being supplied in his interest, and on their being in some sense wholesome. One might say that the patient can expect that, cost aside, nothing will be done that will not be in his best interest, assuming of course that he has come for what is in the doctor's bag of tricks. If it is not, he will expect to be turned away with a polite but firm "I'm sorry." Of course, each purveyor may have a limited bag of tricks, so that the patient may have to go to another purveyor. But in this the physician is duty-bound, that is, contractually bound, to aid him or to pass him on to the right purveyor.

The physician for his or her part should be operating with the confidence to which being licensed attests. He should believe that he has the skills it attests to and that he is bound to provide them on request, cost aside, and bound as well to desist and refer to another if he does not have those skills. He or she has prior contracts with the profession and the state to act within the bounds of his license, his professional imprimatur. He may not morally violate that contract, for it is implicit in the offer he makes to every patient. By holding himself out as one who provides medical care, he signals to the world that he knows what he is doing and that he is guided by the standards of the guild that successfully bars others from holding themselves out as healers of this sort. That is why confidentiality, as well as all the other well-known traditions of the profession, can be assumed.

Hospitals as Third-Party Guarantors. But so far in this discussion another important party has been ignored. Because of the complexity of modern medicine, it turns out that much that can be done must be done in larger institutions, particularly hospitals. The physician may not, because of the standard of care now generally acknowledged, do without the hospital what in former times he might have done. He is barred from the free-wheeling practice of medicine. And the institutions themselves (for many of the same reasons as are cited above) became another group of third-party guarantors of the physician-patient contract. Hence, implicitly, when the patient seeks medical help, he believes, and he is entitled to believe, that the physician's aid is guaranteed, certified, warranted to be wholesome and, to the extent possible under the circumstances, performed in his interest, for his ultimate good. So, of course, there really is no reason for the patient to overly concern himself or herself with the particulars of care.

The Patient's Knowledge of Quality of Care. If it were not for the suspicion that not all physicians are equally competent and not all physicians see themselves as equally bound by the criteria and rules of quality medical care, the patient would be as entitled as the opener of a can of tuna fish to use the service just as the practioner provides it and not as the purchaser chooses or might wish to use it. The patient is not, and generally cannot be, in a position to know what he is getting, what he should be getting, what is the best, what is adequate, what is substandard. Such knowledge (from the patient's point-of-view) is esoteric, beyond his ken, and he relies and is entitled to rely on what is held out to him. And the doctrine of estoppels holds the physician is not entitled after the fact to say he did not know or did not imply he was able, or did not mean to say that his actions would be in the patient's best interest. Nor can a hospital be heard to say that it gave less than the best because it was not able, did not promise, had no contract, did not think the patient would rely on it.

Resistance to Care. In all of the above I have left cost out because all the patient promises to do is pay the bill and aid in his own care, or at least not thwart the care extended. If he does not pay or he resists being cared for, then he, for his part, breaches the contract he has with the physician, the hospital, and the profession. He, of course, can be made to pay by the courts, but they have only a limited ability to force the patient to assist in his own care. Sometimes the court will step in and force the patient to take the optimal path, but often not. The patient's autonomy provides a ground for him to break off the contract at nearly every point. But, if he does, the responsibility for the consequences is all his. If he does not break the contract, the responsibility for any avoidable bad consequences belongs to the physician, or the hospital, or the profession (which licensed an incompetent), or perhaps sometimes even the state for licensing those that it ought not to have licensed.

The Quality of Third-Party Guarantees. I am assuming here that there is something to doctoring. If the state also licensed astrologers, I would begin to have my doubts about the value of the state's guarantee. Of course I do have my doubts about the profession's guarantee. I know from law and education that many are licensed who are incompetent or become incompetent. Professions notoriously do a bad job in policing themselves; they should be held to a higher standard, and to do so we should hold them collectively responsible for the failings of their fellow artisans. We do that, to some extent, through the high cost of malpractice insurance, penalizing all for the faults of a few. In law we do it for criminal theft by lawyers by providing a fund to compensate victims that is paid for by all lawyers (at least in New York State). Neither is quite enough, for what we need is a more constant monitoring of the care provided. Physician review both by states and insurance companies also aids in this endeavor, so I do not mean to say there is no policing; but it is not remarkably effective, and it is also not well known. Were it effective and well known, the patient would be fully entitled to rely on the care extended and to trust that there is good wholesome tuna fish in every can.

The Implicit Contract between Physician and Patient. Some will say that the picture I paint is unrealistic. Patients differ, diseases differ, much is not known, each plays an enormous role. All of that is true. Patients are not guaranteed health, or recovery, or youth, or beauty. What they are guaranteed is the health provider's best efforts, a level of concern directed to his interest, and a level of quality that is informed, able, and relevant to his case. Less than this is a breach of the implied contract between them, just as a breach of the implied duty of confidentiality would be. No one is compelled to be a health provider. If anyone is not willing or not able there is much else in the world to do. One could become a philosopher; the pay is not so good, but the duties to others are fewer and, after all, one does not expect much of them. From physicians we expect a great deal; we place our lives at their disposal, and we have a well-founded belief that they will take them as seriously as their own lives—that is part of our (society's) implied contract with medicine.

The Contract Model of the Doctor-Patient Relationship

A Critique and an Alternative Ethics of Responsibility

John Ladd, Ph.D.

My thesis is that the contractual model of the doctor-patient relationship, when taken as an ethical model, is incoherent, inappropriate, and misleading, and is therefore morally unacceptable (1–4).

Since there is no single, crystal-clear, authoritative version of the contract model of the doctor-patient relationship for me to focus on in my attack on the ethical adequacy of that model, I shall have to proceed indirectly. Accordingly, my strategy will be to review a number of typical and ethically relevant features of contractualism in general, in the hope thereby of being able to isolate facets of the contract notion that are or might be relevant to an understanding and critical evaluation of the contractual model as applied to the doctor-patient relationship. Although some of the contentions in my analysis might not appear to be germane, they are intended to be provocative. In particular, they are intended as a challenge to those who want to defend the contractualist position to explain why the consequences and implications that I attribute to the contract notion in general do not in fact pertain to the contract model of the doctor-patient relationship.

Two Methodological Caveats. Before turning to the substantive part of my discussion, I want to mention two caveats, two traps to be avoided:

The first trap is the choice of an ethics by default, as it were, that is, the assumption that one has to choose between a limited set of ethical options, for example, between paternalism and contractualism or between a consequentialist and a deontological ethics. I call this the "fallacy of limited options." In fact, there are many other available theories about the doctor-patient relationship, and if none of them is found to be satisfactory, common sense would dictate that we ought to start looking for new ones.

The second trap is mixing up ethics and law. The confusion of the two leads to looking to the law for the answers to ethical questions. This trap might be called the "fallacy of the legalization of ethics," the fallacy of deriving ethical conclusions from legal premises alone.

In the rest of this essay, I shall assume that the issue under discussion, contractualism, is an ethical, not a legal issue.

Background. A quick look at the historical background of contractualism may help to highlight some of the essential facets of the theory.

The obvious historical antecedent to contractualism of the kind under consideration here is the theory of social contract, as represented by Hobbes, Locke, and others. The basic motivation of the social contract theory was to develop an answer to authoritarianism, particularly to the notion of the divine right of kings.

In its best forms, the social contract theory is antiauthoritarian, individualistic, and egalitarian. And these are the obvious features of the contract idea that those in quest of a model of the doctor-patient relationship find attractive. Thus, contractualism might be viewed as a modern response to the exaggerated claims of medical pa-

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ternalism that suppose that doctors have a sort of God-given right to rule over their patients.

There are other aspects of the social contract theory, however, that are more problematic, such as questions about when, how, and why the original contract was made. Historically, in order to save the theory, an extensive mythology had to be invented to make things come out right. Thus, for example, rather than being actual historical events, the contracts were held to be fictitious, tacit, implicit, or hypothetical. The same old questions about the origins and basis of the contract have come down to modern versions of contractualism, including the contractualist model of the doctor-patient relationship. We find again the same need for a mythology to rescue the basic idea.

Contractualism, or "contractarianism," as it is now called, has had a revival in contemporary moral philosophy. It provides the cornerstone in the otherwise diverse theories of philosophers like Rawls, Gauthier, Scanlon, and others. The motivation of these philosophers for reviving contractarianism is, however, somewhat different from that of the earlier historical theorists. Their aim is more theoretical and is largely directed at framing alternatives, as for example to utilitarianism and intuitionism.

For present purposes, perhaps the chief point about all these different forms of contractualism, old and new, is that they share the basic assumption that the parties to the original contract are to be conceived as self-interested individuals who are "mutually unconcerned (do not care how others fare)." Other-regarding interests and concerns are automatically excluded in the original formation of the contract. I shall return to this point later.

Questions. Bearing in mind that we are concerned here with what might be called "moral contracts," rather than legal contracts, there are still a number of questions that need to be asked about such contracts, actual and alleged. I shall simply mention but not try to answer any of these questions here.

Who are the parties to the alleged contract? How is it created: is it historical, fictitious, hypothetical, constructive, tacit, implicit, and so on? What kind of contract is it? What is it a contract for? What is promised? What is the quid pro quo for each party? What are the goods received and exchanged by the parties? When is the contract fulfilled, terminated, and so on? What are the sanctions for violating the contract? And last but not least: how does the contract affect the obligations and rights of third parties? I shall leave all these questions to others to answer.

Ethical Aspects of Contracts In General

To begin with, contracts are social mechanisms for creating new rights and obligations, over and above any other rights and duties that individuals may already possess. The contract model is situationally specific and specific to the individuals involved, who, as just mentioned, generally have no prior rights or obligations to each other with regard to the matter at hand. For example, in contracting to have my house painted, the painter, who has no prior obligation to me, acquires the new obligation to paint my house and I, who have no prior obligation to the painter, acquire the new obligation to pay him the amount agreed upon. Prior to the contract, neither of us had these obligations.

The plausibility of the contractual analysis of the doctor-patient relationship rests in large part on the consideration that when this relationship is established, new rights and obligations come into being that did not exist before. Thus the obligation of a doctor to treat a patient is not a consequence of a general duty to help others; rather it is an obligation that first comes into being when the relationship is established. Contractualists claim that the mutual obligations of doctors and patients come into being through the making of a contract.

It should be noted, however, that because contracts are agreements and establish new relationships, it does not follow that all agreements are contracts or that all new relationships, and their corresponding mutual rights and obligations, are created through contracts. This is an obvious non sequitur.

Another general fact about contracts is worth noting. Not only do contracts create rights and obligations de novo, so to speak, but they generally also stipulate the terms of the obligations, that is, what is to be given and what is to be received by each of the parties. Thus, it is the nature of contracts in general to create both the basis and the content of the mutual rights and obligations—at least in theory.

Just as there is a certain arbitrariness about whether there will be a contract or not, what goes into a contract and what is left out is also arbitrary, inasmuch as it depends on what is agreed to by the contractees. Within the limits of the law, custom, and general morality, there is nothing in principle to bar the contractees in a medical contract from providing for quite idiosyncratic requirements. Whimsical contracts are, at least theoretically, still contracts. Does the alleged doctor-patient contract permit whimsical contracts?

One obvious answer to this last question is that the terms of the contract are set by the profession or other social institutions. In other words, professional standards determine what is or is not to be expected in the doctor-patient relationship. But this, in turn, suggests that the contractual aspect is redundant.

A second side of the contract model, in this case a presupposition, is the principle of freedom of contract. This principle requires that the parties to a contract enter the contract freely and willingly, in that the prior bargaining is unencumbered and the parties bargain as equals. Effectually, this means that either of the contractees must be in a position to refuse the offer of a contract made by the other.

Here we must ask: Is the required freedom and equality possible in the doctor-patient relationship? Are patients really free to refuse, and do they bargain with doctors as equals? Can the contractual model be made to fit without introducing ad hoc and mythological assumptions, such as the presumption that the patient, who is in fact unconscious, can be taken to have agreed to the contract because he would have done so had he been conscious, or because any rational person would agree to such a contract? But, I submit, that sort of mythology destroys the basic idea of a contract as a binding agreement entered into freely among equals. I need not labor this obvious difficulty.

A third side of the idea of a contract is that it brackets questions of motivation. Once the contract has been made, the source and rationality of the contractee's interests are excluded from consideration. As long as they are not provided for in the contract, the needs of a patient and the desire of a doctor to help the patient are irrelevant to what is considered to be an obligation or a right stemming from the contract.

I shall return to this point about the exclusion of motivation later.

The Ideology of Contractualism. Contractualism, more specifically contractarianism, as an ethical theory characteristically presupposes a particular view of human nature, of human relations, and of society, which, following Gauthier, I shall call its "ideology."

The ideology in question starts with an atomic individualism of some sort or other that maintains that society consists of self-interested individuals. The actions of these self-interested individuals are coordinated for mutual self-interest through contracts that they make with each other in order to improve their situation. In the final analysis, self-interest is the only rationale for self-interested individuals to enter a contract.

According to the contractualist ideology, the social bonds (that is, binding moral relations) between individuals in society are contractual in nature, that is, they are created and maintained by contracts. Affective bonds, on the other hand, such as mutual concern or love, are either adventitious, irrational, or morally irrelevant. The nuts and bolts of the system are the contracts; the rest is window-dressing or sentimentality. Only contractual bonds are strictly morally binding. There is no way in which affective bonds that are noncontractual can be morally required or, indeed, can enter into the moral picture at all.

Finally, it should be acknowledged that, when all is said and done, the paradigm of contractual agreements is the kind of commercial contract that incorporates financial arrangements of some sort or other or exchanges of goods and services. In spirit, if not in intent and effect, contractualism represents commercialism. As such, it turns doctors into merchants and entrepreneurs and patients into consumers and purchasers. (The comparison with bakers is classic.) In the end, perhaps, the commercial implications of medical contractualism make it a theory for the benefit of the rich that leaves the poor out in the cold.

The Bracketing of Motivation. As I have already pointed out, according to the contract model, motivation is irrelevant, or even excluded as unnecessary or befuddling. To begin with, in the original bargaining position, contractarians like Rawls and Gauthier stipulate the condition of "mutual unconcern" among the bargainers. After that, the only moral requirement is that contractees perform their contracted obligations, and why they do so, their motives, are morally irrelevant. For contractualism, the motivation of the contractees is relevant only because it tends to make predictions about their performance more reliable.

By all accounts, then, contractualism is a hardheaded theory. It makes the motives of doctors morally irrelevant as long as they keep their side of the contract—for whatever reason. In other words, the moral basis of a doctor's duty to care for patients is not that patients need the care but that the doctor is bound by a contract.

It follows that, apart from being stipulated in some indirect way in the contract, any sort of appeal on moral grounds to the needs or suffering of a patient or to the requirement of sympathy, compassion, care, or concern on the part of the doctor is not part of the doctor-patient relationship. If doctors show such concerns, their doing so is *supererogatory* and they are like heroes or saints acting "beyond the call of duty." In this regard, the doctor-patient relationship is comparable to the buyer-seller relationship in a store: the buyer's motives are irrelevant as long as he pays, and the seller's motives are irrelevant as long as he delivers the goods. Friendly smiles and concerns for the other are simply frosting on the cake or good public relations. Giving something away for free makes no sense on this model.

It should be clear by now that contractualism, when applied to the conduct of doctors and patient, is committed to a minimalist ethics, an ethics that consists solely of strict obligations, that is, fulfillment of rights, and acts of supererogation, as for example acts of kindness. By the same token, common garden-variety virtue is not a moral requirement, for on a minimalist view like contractarianism, a good doctor is simply an honest one, who keeps his promises. There is no obligation to provide "extras," like being a "nice" or "friendly" doctor, much less to feel sorrow or shed tears when a patient dies—unless, of course, it is good for business.

The moral weaknesses of the contractual model should now be amply evident. They may be summed up by saying that it dehumanizes the doctor-patient relationship and neglects the important and valuable aspects of that relationship that revolve around caring for patients and healing them, activities that may be regarded as ends in themselves rather than simply as means to fulfilling a contract and making money.

We need another kind of theory.

Another Approach: The Good Doctor and the Ethics of Responsibility

In this final section, I want to move to another level and try to sketch a different and I hope more adequate view of the doctor-patient relationship. The new approach might be called a "virtue ethics," although the conception of virtue that I have in mind is considerably different from traditional theories of virtue, like Aristotle's, which identify it as a quality of persons (character) rather than of conduct and relationships. The kind of virtue ethics that I find most satisfactory for analyzing the doctor-patient relationship focusses on the concept of a good doctor as a practitioner, which in turn hinges on the quality of the mutual relationship between doctors and patients and the mutual responsibilities that the relationship implies.

The version of virtue ethics that I propose here rejects the view that all duties are contractual or rights-based (that is, strict duties), and holds instead that there are also duties of the kind that Kant calls "duties of virtue," duties that are defined by motivation, such as care, concern, and compassion. These duties relate to other-regarding actions directed at ends such as the well-being of others and the mitigation of suffering. Health, of course, must be included here. Duties of this kind arise in response to specific needs of particular persons in specific interpersonal contexts like the doctor-patient relationship. Accordingly, there are specific duties of virtue associated with being a good doctor, that is, duties of care, compassion, and concern in response to the needs and sufferings of patients. The kind of duties involved here belong under an ethics of responsibility. (Responsibility, as used here, is a virtue, just as its opposite, irresponsibility, is a vice.)

To be a good doctor, therefore, means to take responsibility for one's patient. Doing so is a requirement of virtue as applied to the conduct of professionals and others who have a special relationship to them, such as patients. As such, the virtue ethics in question, unlike the Aristotelian version, is situational and interpersonal. It might be called *modal.*

The kind of virtue ethics proposed here is egalitarian rather than elitist. For among other things, a moral (or virtuous) doctor-patient relationship requires that doctors and nurses treat patients as persons—ends-in-themselves, as Kant would say. A patient is not just a body or a case, or even a slave or an animal, to be fed, treated, and ordered around. The relationship between doctor and patient is a social relationship between persons as equals, which as such requires mutual consideration, respect, trust, truthfulness, and, where feasible, shared decision-making.

Thus it can be seen that, like contractualism, a virtue ethics or, more particularly, an ethics of responsibility preserves the principle of equality and antiauthoritarianism. But unlike contractualism, it centers more directly on the needs of the patient and the care and concern of the doctor and on the relationship that grows out of them. It builds on the principle of humanity.

For all these reasons, as well as for many others, I propose that we try to develop an ethics of the doctor-patient relationship along the lines of an ethics of responsibility, which emphasizes the tenor (mode) of the relationship, rather than settling for a contractualist ethics simply because it is assumed to be the only option left after paternalism has been discarded.

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The Physician's Virtues and Legitimate Self-Interest in the Patient-Physician Contract

LAURENCE B. MCCULLOUGH, PH.D.

THE BIOETHICS literature abounds with discussions of the patient-physician contract. Almost exlusively, these discussions concern the physician's ethical obligations to his or her patient. Increasingly, ethical obligations of physicians to third parties to the patient-physician relationship must also be considered. The physician's ethical obligations to his or her patients are typically understood in terms of the by-now familiar ethical principles of beneficence, nonmaleficence, and respect for autonomy (1). The physician's ethical obligations to third parties such as families of patients and the institutions that organize, deliver, and pay for health care are typically understood in terms of the principle of justice (1). This much is familiar territory. Interestingly, it is a territory still marked by a great deal of contention and disagreement. This is as we should expect, given the complexity of the patient-physician relationship and its embeddedness in a complex web of third parties. This much is clear: the physician is the agent not only of patients but also of third parties. The obligations that the physician has to both must be carefully identified and negotiated in a thoughtful manner.

It will come as no surprise that many physicians conclude that this discussion is one-sided. As one of my colleagues puts it to me, regularly and with no little exasperation, "Physicians have all of the obligations and patients all of the rights!" Even a cursory reading of the bioethics literature, not to mention even the slightest brush with the law of malpractice, gives no other impression.

It is long past time to redress this imbalance, and I want to take some tentative steps in that direction. I say "tentative" steps, because the territory that I intend to chart is little explored and little understood. The opportunities for error and confusion, therefore, abound. As philosophers like to say, there are many conceptual thickets in such an uncharted territory. Let us see how far we can explore without too substantial a loss of dermal protection.

The Physician's Virtues: Self-Effacement and Self-Sacrifice

In my own view—and the view of many in the field of bioethics—the patient-physician relationship finds its ethical basis or foundations in the character of the physician, in the physician's virtues (2). The virtues are those habits or traits of character that blunt one's self-interest and direct one's concern to the interests of others. On this basis, the physician's basic ethical obligation to the patient can begin to be identified. That obligation is to protect and promote the interests of the patient and of third parties (3). The ethical principles are necessary to fill in the detailed content of this general ethical obligation in concrete clinical situations. This blunting of the physician's self-interest also inclines the physician to fulfill his or her concrete ethical obligations to the patient.

Two virtues seem fundamental. The first is self-effacement, which blunts self-interest and fo-

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cuses the concern of the physician on the interests of patients and third parties. Self-effacement does so by negating the adverse impact on the physician's attitudes and behavior of differences between the physician and the patient that should not count in the care of the patient. Differences in such matters as socioeconomic class, education, race, gender, culture, religion, language, manners, hygiene and—as the great physician-ethicist of the Scottish Enlightenment, Dr. John Gregory, called them—the "thousand peculiarities to which the sick are subject" (4) are to be put aside, erased from the physician's scope of concern. The physician's concern is thus directed away from mere self-interest—this patient is drunk or smells or does not seem to understand what one has to say—toward the interests of the patient.

Taking care of patients is demanding and rewarding work. Taking care of patients can also be exhausting, and sometimes even dangerous. Demanding work and personal risk call for sacrifice on the part of the physician—sacrifice of time, energy, obligations to others, and even health and life. The latter sacrifices, by the way, were not introduced by HIV or HBV—as any emergency department or military physician over the years could well remind us all. Self-sacrifice requires physicians to accept risks to themselves and to display a disciplined calm in that acceptance (2). In this way mere self-interest is blunted in favor of protecting and promoting the interests of patients and third parties.

Now, self-effacement and self-sacrifice can be tyrannical virtues—and thus vices. That is, virtues can be transformed into destructive traits of character, if they are taken to be absolute, when they are taken to admit of no limits in the moral lives of physicians. Some have asserted such a view. Pellegrino, in speaking to the obligations of physicians to take personal risk in the care of HIV-infected patients, writes: "To refuse to care for AIDS patients, even if the danger were much greater than it is, is to abnegate what is essential to being a physician" (5). This sort of claim betrays a profound misunderstanding of self-sacrifice and of the virtues generally.

The virtues blunt self-interest but in doing so they cannot eliminate all self-interest. That is, not all forms of self-interest that might be opposed to the interests of patients and third parties amount to mere self-interest or, more bluntly, selfishness. The mistakes that Pellegrino makes are two. First, he fails to recognize the category of legitimate self-interest on the part of the physician. Second, he fails to recognize the compatibility of legitimate self-interest with the virtues of self-effacement and self-sacrifice.

The Role of the Legitimate Self-Interest of the Physician

The physician's legitimate self-interest, I submit, must be taken into account in the ethics of the patient-physician contract. Physicians' legitimate self-interest may even serve as the basis of ethical obligations on the part of patients and third parties to physicians, as I hope to show. Before exploring why this may be the case, however, we first need to get clear about the concept of the legitimate self-interest of the physician.

In the bioethics literature this concept has not been accorded the careful consideration it deserves. And so we enter largely uncharted philosophical and clinical territory. Legitimate self-interest can usefully be understood to comprise a continuum of ethically significant features of the physician's moral life, considered as a whole.

Mundane Requisites for Good Patient Care. First, physicians can properly claim a legitimate self-interest in the requisites for good patient care in their own day-to-day lives. I have in mind here such apparently mundane, but in truth ethically significant, matters as the time to study, reflect, and learn and the time to rest and to maintain an alert mind, to name only two that come quickly to mind. That is, some forms of self-interest should count as forms of legitimate self-interest when those forms of self-interest can be tied to the necessary conditions for providing good patient care, day in and day out, over a lifetime.

Obligations to Persons Outside the Medical Network. Second, physicians are bound by ethical obligations to people other than patients or third parties, for example spouses, lovers, friends, children, and neighbors. To be sure, the physician may have freely engaged in the relationships within which such ethical obligations come to life. However, the physician is not morally free to abrogate those obligations without the permission of those affected. Thus, the fulfillment of such obligations is a central feature of the physician's moral identity as a whole person. Such ethical obligations therefore properly constitute, in part, the physician's legitimate self-interests.

Meaningful Nonmedical Activities. Finally, legitimate self-interest also should include those activities that the physician finds to be meaningful outside being a physician and therefore outside the demanding network of obligations to patients and third parties. These are the activities that engage the physician as a "private" person and that also provide him or her deep fulfillment and satisfaction: fly-fishing, attending the opera. They need not, but often in fact do, support and sustain the two types of legitimate self-interest that I have just described.

"Mere" Self-Interest and the Virtue of Self-Effacement. Mere self-interest—"selfishness" seems too harsh a term—comprises those forms of self-interest that cannot be shown reliably to count as one of three forms of legitimate self-interest I have just described.

Self-effacement is directed as a virtue to blunting forms of self-interest that are in almost all cases, I think, forms of mere self-interest. These mere self-interests—for example, petty frustration with the so-called noncompliant patient or anger at bureaucratic hurdles which third parties seem devoted to erecting in the physician's path—can be readily reined in by the virtue of self-effacement. Thus, for the most part, self-effacement is a virtue the moral demands of which should be regarded in clinical practice as routine and nonburdensome.

Anger as Legitimate Self-Interest. There may be some exceptions. Consider the following. Earlier this week a colleague of mine, a pediatric critical care physician, told me of how he had finally had it with a grandmother who was interfering with her daughter's decisions about the patient, the woman's grandchild. This woman was also interfering, sometimes quite obtrusively, with the care of the child by nurses, physicians, and technicians. She was a general nuisance most of the time, something worse sometimes. Over many days, he said, he asked this woman to appreciate the difficulties she was causing, he tried to understand her needs and respond to them, and he asked her please not to do what she was doing. Finally, he said, that morning, after a particularly unpleasant event, he had told her, "Back off!"

This, of course, was an expression of anger. As such, it was clearly meant to focus this woman's mind and change her behavior. One might ask, are there justified expressions of anger on the part of a physician? After all, is anger at the surrogates of pediatric patients—or at patients themselves—not a form of mere self-interest that self-effacement is supposed to blunt? I am not so sure, especially when such expressions of anger are undertaken as last-ditch efforts to get someone's attention and change behavior that is at risk for adversely affecting the patient. Sometimes, expressions of anger can succeed in accomplishing these goals when nothing else has.

If this line of reasoning makes sense, then the following can be said with some confidence: patients or patients' surrogates have no right to take umbrage at legitimate expressions of anger or other forms of legitimate self-interest rooted in the well-being of patients on the part of physicians. Indeed, patients and their surrogates are ethically obligated to attend to these forms of legitimate self-interest and act on them, one might say. After all, it seems, patients and their surrogates owe their physicians a certain level of serious attention and consequent intellectual and behavioral discipline. This is especially true when the stakes (of allowing undisciplined behaviors to go unchecked) are high for patient care. It would be worth inquiring at more length into other examples of legitimate self-interest that the virtue of self-effacement should not blunt. But this is a large topic and beyond the modest scope of this presentation.

Negotiating Conflicts between Self-Sacrifice and Legitimate Self-Interest The virtue of self-sacrifice also affects both mere and legitimate self-interest. If the care of a particular patient requires only a little extra time or if the hospital requires paperwork to be properly completed so that it can routinely collect payments and secure the financial base of its mission, expecting the physician to be self-sacrificing seems almost certainly to be reasonable. When self-sacrifice involves risk to the physician's health or life, self-sacrifice aims at something more, the regulation of the physician's legitimate self-interest, because risks to health and life involve all three forms of legitimate self-interest. A question that must be addressed in the ethics of the patient-physician contract is, Must legitimate self-interest always be sacrificed?

One thing seems clear from the outset: the virtue of self-sacrifice cannot be understood to be absolutely controlling of the physician's thought and behavior, as Pellegrino would seem to have it. This is because legitimate self-interest should always be taken into account by the physician in the process of determining the proper moral demands of the virtue of self-sacrifice.

There is no easy algorithm for negotiating conflicts between self-sacrifice and legitimate self-interest. In part, this is because there is no uniform set of legitimate self-interests that characterizes each and every physician. Some are married; some not. Some have or wish to have children; some not. Some have weighty obligations to family, and may, for example, be caring for a frail parent at home; some have routine obligations to family. Some are devoted full-time to medicine; some cannot flourish absent an occasional foray in a trout stream or an evening of Puccini. As a consequence, the process of negotiating conflicts between self-sacrifice and legitimate self-interest will allow of some variability.

Some rules of thumb, though, seem reasonable. First, every effort should be made to reduce unnecessary impositions on legitimate self-interest in day-to-day clinical practice. I have in mind here such matters as making universal infection control a reality, establishing rational and fair staffing and call schedules. Second, the physician needs to distinguish carefully between his or her mere and legitimate self-interests. When in doubt the physician should favor the conclusion that the self-interest in question should be treated as mere self-interest. Third, one's judgment of the resolution of conflicts between self-sacrifice and legitimate self-interest should be tested for its intellectual rigor and reliability against the considered judgment of colleagues.

Fourth, institutional practices and policies need to be carefully reviewed, to determine whether they impose a tyrannical concept of self-interest on the one hand or encourage mere self-interest, for example in remuneration for its own sake, to rule the roost. Both, I believe, are a threat to the moral life of the physician. Institutional third parties would therefore seem to have an ethical obligation to protect and promote both the virtues and the legitimate self-interests that are essential to the moral lives of physicians. In other words, institutional third parties have an obligation to respect the autonomy of the physician when that autonomy is exercised on behalf of legitimate self-interest. In my own view, institutional third parties for the most part have yet to acknowledge this as among their ethical obligations. We are all of us, patients and physicians alike, at moral peril as the result.

Finally, a physician who reliably reaches the conclusion that a conflict between self-sacrifice and legitimate self-interest should be managed in favor of legitimate self-interest should explain the conclusion to the patient. After all, patients, too, have a vital stake in sustaining the moral lives of their physicians. Too, one might argue that respect on the part of the patient for the autonomy of the physician should include respecting the physician's legitimate self-interests. This would be a direct parallel to the physician's autonomy-based obligation to respect the patient's legitimate interests.

Summary

I will be the first to admit that we are now well into uncharted territory of the patient-physician contract. I also detect missing stretches of my dermal layer and you may spy some that I have yet to notice. In any case, I put to your serious consideration the proposal that part of the patient-physician contract must include respect for the legitimate interests of the physician by patients and third parties.

The virtues of self-effacement and self-sacrifice and the concept of legitimate self-interest help us to understand in concrete, clinically applicable terms what such respect means in practice. That respect will, I think, be expressed with some variability, because there is no simple algorithm for negotiating conflicts between legitimate self-interest and the virtues of self-effacement and self-sacrifice.

One important consequence of this moral variability is that the patient-physician contract and the virtues that sustain it will not yield to a single, finally authoritative account of how such conflicts should be negotiated. Instead, as we turn more attention to these matters, we will, I believe, discover that there is a range or continuum of ways in which the management of such ethical conflict can reliably be understood in the patient-physician contract. Rather than a single account of the ethical dimensions of the patient-physician contract, we should expect to develop a range of reliable accounts. A kind of rich and engaging moral pluralism should thus govern our understanding of the ethical dimensions of the patient-physician contract. The interesting and important issues will concern the boundaries of that moral pluralism: which accounts of the contract should count as ethically reliable and which should not? I hope to have made a small start in the direction of the larger and certainly more daunting task of addressing this important question.

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Consumerism Rampant:

A Critique of the View of Medicine as a Commercial Enterprise

Daniel A. Moros, M.D.

The title of this conference, "Whose Contract Is It Anyway?" immediately reminds us that many parties have an interest in the conduct of the relationship between doctor and patient. In addition to the two principles, others include the family, the state, insurers, medical institutions such as hospitals and health maintenance organizations, and at times, the employer. Clearly the more parties granted standing, the greater the potential for conflict. Although we have always known that in a fee-for-service system there is a potential conflict between physician and patient, in recent years our awareness of conflict within the medical setting has been heightened by such factors as the efforts of the state and third-party payers to limit medical costs, and differing views about the proper application of new technologies.

Since interests may conflict, we are challenged to characterize the doctor-patient relationship and explicitly identify the legitimate expectations and duties of the parties. It has certainly proven easier to describe conflicts than to state in positive terms what the doctor-patient relationship ought to be. At first glance the title of our symposium seems to presuppose that the language of contracts will accommodate the reality of this relationship. However, although the language of contracts is remarkably flexible and can be applied to a broad range of social interactions, a question remains as to its adequacy for capturing many essential features of the physician-patient relationship. In exploring this question we must avoid unwittingly simplifying our view of the physician-patient relationship in order to accommodate our notion of a contract. Unfortunately, this is a common error, and an overly simple view of the medical enterprise and the doctor-patient relationship is presupposed by much current bioethical discussion as well as health-related legislation and case law.

Five Oversimplifications of the Medical Enterprise

I start, therefore, by outlining five widely held, interrelated perspectives about medical care that I believe lead to a pervasive misunderstanding of the medical enterprise. In critiquing these five "simplifications," I must also convince you that they are, indeed, widely held, and that I am not attacking a straw man.

The Commercial Metaphor. The first simplification, which may be labelled the "commercial metaphor," is the widely held view of medicine as mere commerce and of patients as health-care consumers. I suspect that within our society the commercial metaphor is so powerful and entrenched, in the form of legislation, regulations of federal and state authorities, case law, and institutional policies, that remarkably few clear and explicit alternative images are available. Indeed, I would suggest that as uncomfortable as many physicians are with this commercial image, it has nonetheless been implicitly embraced by the profession itself.

In support of this contention, consider the following passage from a U.S. Appeals Court decision of Feb. 1990 (1) upholding an earlier district court's judgment in which the AMA was "found guilty of a conspiracy to destroy the competitive profession of Chiropractic":

> Relief here is provided not only to the plaintiff chiroprac-

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> tors, but also in a sense to all consumers of health care services. Ensuring that medical physicians and hospitals are free to professionally associate with chiropractors (e.g., by the publication and mailing of the order to AMA members), likely will eliminate such anticompetitive effects of the boycott as interfering with the consumer's free choice of choosing a *Product* (*health care provider*) of their liking [italics added].

Notice that there is no discussion here of patients and their needs or doctors and their duties—only of consumers and their likings. The commercial metaphor is not simply a matter of the doctor as tradesman, or, to adopt the language of the court, the doctor as "a product"—there is also the image of the patient as a consumer of medical products and services. Similar-sounding passages can be found in Federal Trade Commission rulings eliminating restrictions on physician advertising.

Linked with this commercial view of the physician-patient relationship is a rather simple notion of the medical enterprise which has been dubbed the "autonomy paradigm" by Jennings, Callahan, and Caplan in their 1989 paper, "Ethical Challenges of Chronic Illness" (2). In this paper the authors critique "three interrelated notions [or simplifications] that form the conceptual infrastructure of most contemporary bioethics":

- A medical model of disease which views illness "as a threat that suddenly intrudes upon a preexisting condition of health and wellbeing" (p. 9). "Here illness is seen as an alien threat to the self, and the goal [of medicine] is to defend and restore the self by curing or compensating for the illness" (p. 8).
- An individualistic view of the person in which "autonomy means freedom from external limits or constraints. In this perspective, the autonomous self . . . is independent of and prior to its social milieu and its bodily condition" (p. 8).
- A contractual model of the physician-patient relationship. According to this view "the patient is a rational, self-interested subject who, threatened by illness, voluntarily enters into a contractual agreement with a physician (or other health care provider) and temporally submits himself or herself to medical authority in order to combat the illness" (p. 8).

The authors maintain that these perspectives have "become institutionalized in health care delivery through the influence of court rulings, government regulations, and the organizational policies of hospitals and other health care facilities." Are they correct? Do these three perspectives indeed capture much of our society's view of the medical enterprise?

The Medical Model of Disease. Consider the medical model of disease. Something goes wrong, you fix it, and that represents a service for which third-party payers will reimburse. Someone has a symptom, you examine the person and make a diagnosis, and again the insurance company will pay. You do not make the diagnosis but order another test; they'll pay. Order five tests when one would have done if only you knew how to take a better history from the patient (or were willing to devote the necessary time to obtaining a history), and the insurance company will pay. Make the diagnosis quickly and expeditiously, and they will pay less. Write on the insurance form "no evidence of neurologic disease, would not do any further testing at this time," or write "well-baby examination" or "depression with somatization" (assuming you are not a psychiatrist) and you will often go begging for your money. Talk to a frightened patient for 20 minutes at 10 PM or spend 30 minutes in discussion with a patient's sibling who calls from San Francisco—forget about billing. This is the medical model of disease. You may be judged for your competence and compassion, but you get paid only for curing or active attempts to do so.

A Highly Individualistic Notion of the Self. How widely held is the highly individualistic notion of the self? We increasingly see within our society an emphasis on conflict of interest between individuals, as opposed to bonds forged by shared experiences and common goals, hopes, and values. We live with increasingly complex regulations concerning child abuse, spouse abuse, elder abuse, and so on, as if interests can be defined in isolation. I am not disputing the value of such regulation. However, I am suggesting that our relative ease in talking about rights, which emphasize the discreteness of individuals, and our difficulty in talking of duties, which inevitably emphasize the interconnections of individuals, is part of this highly individualistic notion of the self.

Viewing the Physician–Patient Relationship as a Commercial Contract. As for the contractual nature of the physician-patient relationship, I think both the title of our conference and the language of the Federal Appeals Court quoted above testify to the pervasive influence of this simplification.

Identifying a Statement of Preference with Autonomy. The fifth simplification, which I discuss more fully below, is the tendency to disconnect the notion of autonomy from the notion of rationality and to focus instead on the mere statement of a preference—that is, the identification of a statement of a preference with an autonomous decision.

Critique of These Oversimplifications

Simplified descriptions are not necessarily bad. Ultimately they must be judged on the basis of how usefully they direct our thinking and how seriously they mislead us. Although I hope to illustrate some of the deficiencies of these simplifications, I want first to emphasize that these are not five random, disconnected perspectives, but rather that they hang together and support each other and are ultimately components of a gravely deficient vision of medicine. The commercial metaphor requires a simple notion of medical services (to wit, the medical model of disease), a simple notion of the contracting parties (conveniently provided by the highly individualistic notion of the person), a limited notion of physician duties (provided by focusing on expressed preferences rather than needs or "what is right"). With this vision in place, the physician-patient relationship indeed appears to be a straightforward commercial contract.

Shortcomings of the Medical Model of Disease. To demonstrate the inadequacies of this vision, let us begin with a critique of the medical model of disease. For heuristic purposes I want to broadly divide medical intervention into four categories: acute care and chronic care, each of which is either curative or noncurative. The medical model of disease applies, at most, to circumstances of acute care associated with relatively rapid cure and misdirects our thinking about most of the rest of medicine.

The doctor provides acute care to many individuals—young, presumably "normal" and healthy; elderly, independent but fragile; persons with ongoing, identifiable but at the moment quiescent illness; other persons struggling with active disease and disability. In this latter group, new difficulties may be part of the ongoing disease process (as when a person with pulmonary disease develops an acute pneumonia) or some unrelated problem. When a surgeon treats a trauma or burn patient, a classic example of acute care, and amputates a limb or devotes years to reconstructive surgery to create a functioning but disabled patient, the doctor can be viewed as acting to preserve life, but certainly not as providing a "cure." When a person treated for carcinoma of the bowel suffers a relapse after appearing to be disease-free for many years, the acute care and apparent cure of the original treatment do not suddenly become redefined as chronic care. And if the disease is truly cured, the yearly follow-up examinations and psychological interventions (perhaps no more than reassurance) are certainly not acute care, but cannot be seen as chronic care for an ongoing disease. Indeed, acute care and curative treatment may require years of attention and monitoring before the results can be known. Similarly, preventive care such as vaccinations, or the treatment of asymptomatic hypertension, or the surgical removal of a lesion that has the potential to become malignant are difficult to label as either curative treatment or chronic care. Although individuals with both acute and chronic conditions may be cured, the medical world does not neatly divide into acute and chronic illness, or curative and noncurative interventions.

Thus the dominance of the image of the physician as healer, as a person who cures acute illness, as opposed to a person of scientific knowledge and technical skills who functions as a rational agent at a time of all illness, belongs to a bygone era when knowledge and doctoring were the province of a priesthood or of "medicine men" (3). This is not to say that the doctor should not usefully exploit his or her priestly, all-knowing persona for a patient's benefit. But science and rationality, that is, proper decision making in the service of a patient, are the defining characteristics of good medicine.

Shortcomings of the Notion of a Discrete Self. I offer two criticisms of the "highly individualistic notion of the self. . . . [that views] self identity, autonomy and interests as conceptually prior to and independent of the encounter with illness" (2). First, people often do not seem to be such discrete individuals, and second, people change under the impact of their experience with illness.

Some examples: A physician taking care of an elderly couple, perhaps a husband disabled by a stroke and a caring wife stretched to her limits, rarely thinks of them as individuals, but as a couple, and it can be difficult to determine where the needs of one end and the needs of the other begin. When people (patients) consider their interests, they often think in terms of other people, so that some patients will not ask for help specifically because they are afraid it will be given too readily and at too great a sacrifice. Some elderly people have saved their money for the next generation and have no intention of squandering their assets on medical care. This is a phenomenon that we encounter less frequently in a setting where a significant portion of the cost of medical care is paid by third parties.

It is also clear that people are changed by illness and that the self is an elusive concept. This applies to more than just the patient with Alzheimer's disease or head trauma who is no longer quite the same, or the patient with cardiac disease or chronic renal disease who may become much more self-preoccupied and at some emotional level less connected with family. Consider the following two cases. In each, a busy active professional who has never before been ill has an acute myocardial infarction, and is focused on returning immediately to work, but for very different reasons. For the first patient, the job requires an early return and to miss work now will involve the loss of great opportunity. For the second patient, to be able to return to work is a way of denying that anything serious has happened. In the first case it may behoove the physician to aid the patient in achieving an early return to work, even at some additional risk to health. In the second case, as the illness is recognized for what it is and the denial confronted, the urgency of the patient's demands subside. In the second case, which person is making the contract—the person of day 1 who has never before confronted illness or the person of day 5 who is beginning to confront things? The changing nature of the self as the patient experiences and confronts an illness and the difficulty in identifying a single person as the physician's sole concern (as in the case of the elderly couple) complicates the idea of clearly defined contracting parties.

Shortcomings in Equating a Stated Preference with Autonomy. The inadequacy of using a stated preference as a guide for the physician's behavior is easily illustrated in another setting. Imagine a 17-year-old child with acute lymphoblastic leukemia (a fatal disease when untreated) whose intelligent and successful parents have always been skeptical about the traditional medical establishment. After watching their child's discomfort following two cycles of chemotherapy (a treatment that offers a greater than 50% chance of cure) they opt for the use of Laetrile (which offers no help in avoiding certain death). The adolescent agrees with the parents' choice.

But the goal of patient and parents is survival. Perhaps they even state that if the doctor could be certain of a cure, they would bear with the chemotherapy. This is a situation in which intelligent individuals have an expressed preference about means—the treatment—that is incompatible with their clearly espoused goal—cure, survival. By and large in our society, the clearly stated preference is credited as an autonomous decision, and the contradiction is ignored. But what ought the physician to do? Should the physician support the choice of means, or do everything possible to reverse this decision?

In this example the parents and patient seem to be basing a decision on an incorrect assessment of the facts. They believe, or hope, that Laetrile will work. The question of what to accept as fact leads to considerations in the philosophy of science that are germane to ultimately defining the role of the physician, but are well beyond the scope of this presentation.

However, we may rewrite this vignette so that the determining factor for the parents is not a belief about medication but rather a concern about the child's pain. What if both parents and child say, "Enough," but the physician knows that the discomfort is bearable because he has seen other children survive and ultimately do well? What if the parents and child are Christian Scientists and do not accept treatment?

The question before us is not to what extent the physician is able to impose his judgment, but rather the logically prior question, To what extent should the physician cooperate with the explicit directions of the patient (and family)? This concern with goals and the moral demands that develop from the physician's understanding of scientific fact goes beyond the range of any simple contract for goods and services.

Abandoning the Consumerist Image

If we abandon the consumerist image of a doctor as an independent contractor in possession of a presumed cure which he sells for a fee to a presumed autonomous and discriminating health-care consumer, we can return to a more demanding notion of a professional in possession of some special knowledge which is to be applied thoughtfully for a patient's benefit. When we emphasize knowledge and introduce the moral requirement that it be thoughtfully applied, the doctor becomes responsible for making a correct technological (medical) decision consonant with a patient's needs and desires. In this setting there may be several medically reasonable choices, and a patient's actual needs or desires may or may not correspond to his or her expressed wishes at a particular moment. Further, there may be a conflict between a patient's goals and her or his assessment of the best strategy to achieve them.

The physician's responsibility at times demands paternalistic action, including a critical initial assessment of whether the patient's statement represents an autonomous choice. A physician may be obligated to interfere paternalistically when the patient is an adolescent, or a young and still developing adult who may never have had the occasion to have seen others manage illness and who now has insufficient capacity or time to consider what must be confronted. Also, in the emergency setting, a severely injured or intellectually impaired adult may require immediate attention and be given little or no role in decision making. Although to some extent such paternalism may be thought of as occurring at the behest of the patient, it is clear that the duties of the physician in the emergency room do not derive from a simple, explicit contract made directly with the patient at the time of illness.

Furthermore, even if a sophisticated contract were able to articulate much or all of the physician's duties and the patient's claim on the physician's time and best efforts, there would remain an unavoidable tension in the idea of contracting for a paternalistic relationship. Indeed, in light of all the considerations above, a fully articulated contract might not be consistent with the degree of discretion required for the satisfaction of a physician's duties.

Knowledge, Thoughtfully Applied: The Trusted Advisor. All this does not erase the possibility that individual relationships may be markedly structured by a set of understandings between physician and patient that seem like a straightforward contract. But even such a relationship exists under the umbrella of a broader set of demands on the physician.

Take as an example an elderly patient who does not want to solicit his children's assistance regardless of the personal consequences. Perhaps this decision places an additional burden on the physician. The physician might disagree with this decision, argue against it, but still honor it. The physician might agree, but argue the point in order to establish that the decision represents the patient's considered judgment. In the latter circumstances the physician's effort might be neither contractually nor paternalistically required. It most closely resembles the behavior of a trusted advisor acting in a relationship involving a considerable degree of intimacy. But is such a relationship included in the contract between a physician and a patient? And why does a physician try to act like a trusted advisor to a new patient? Is it just good citizenship? Is it another form of the obligation derived from the possession of special knowledge? Is the physician indeed obligated to fulfill the function of trusted advisor, or merely required to deliver a properly performed medical task (such as the reading of a chest x-ray)?

Ultimately, the physician's behavior will vary depending on the wishes and understanding of the patient. Furthermore, both the patient and the doctor-patient relationship may change with time, and the duties of the physician may alter commensurately. Thus, even when a more explicit, contractlike arrangement is agreed to at the beginning, if the need for critical decisions arises at a time when the patient cannot participate in reassessing the original understanding, the physician may need to unilaterally decide whether the original understanding is still in effect. This is a circumstance that the physician should strive to avoid. I am not here trying to extend the range of unilateral decision-making by the physician. Rather, my purpose is to illustrate the limitation of the contractual model of the physician-patient relationship and the misrepresentation of medicine embedded in the commercial metaphor.

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The Necessity and the Limitations of the Contract Model

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It seems clearly established at law that physician-patient relationships are regulated and adjudicated by contract law (1). When a doctor's gatekeeper answers the telephone and makes an appointment for a person to become a patient, in that conversation a contract is joined. In a similar way, when a hospital admits a patient, a contract is made.

At law, contracts can be express (and written); or they can be implied (and sometimes spoken). There is no legal distinction between express and implied contracts, once established. They have equally binding contractual force. For example, in each of the cases above, physicians cannot legally abandon a patient.

In a doctor-patient relationship the establishing of a contract also imposes on physicians other legally enforceable duties—duties not established as contractual duties, but duties flowing from the contract. The shorthand idiom for these legal requirements is that physicians must "exercise reasonable skill and care" in response to their patients. These duties are imposed by law, but they are usually defined and given concreteness by the professional ethos of medicine itself. The law undergirds the duty (2); but medical practice gives it content and specificity.

When a patient gets hurt—or better still, when she feels angry, abused, not respected, or emotionally or otherwise abandoned or harmed—she can seek redress for alleged violations of the doctor-patient agreement through "breach of contract" litigation (with the pros and cons of those procedures). Or if she is hurt by alleged failure to exercise reasonable care, she can seek compensation through tort law (with its particular pros and cons). Breach of contract is essentially the failure to deliver a specified service or good. Tort is another thing: a negligent injury, or an injury suffered by the patient, caused by an action or a failure to act by the physician, in violation of the legally defined "reasonable care" (1, pp. 340–371; 2, pp. 253–266; 3).

This arrangement in the law reflects the judicial recognition that contract law, and the model or paradigm informing it, is not a fully adequate model for addressing the complex of human problems exhibited in modern medicine—in modern, technological medicine, which is at once a tragic profession and a moral art (4, 5).

The law recognizes that medicine is not a mere entrepreneurial enterprise—indeed, that it is not in its essence or intentionality a business transaction at all. Going to one's doctor is not analogous to buying a used car. What is happening in the medical clinic is not an arms-length transaction—or it should not be. "Caveat emptor," "Let the buyer beware," the ruling motto of the marketplace, has no place in the tragic profession of medicine, the practice of which is a moral art. "The essential nature of the association between practitioner and patient involves a professional service rather than a sale" (2, pp. 261).

The law itself clearly recognizes all this, which is why certain kinds of contracts that might theoretically be entered into freely by mutually consenting competent adults, without coer-

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cion or deception or duress—where each party voluntarily chooses, out of self-interest, to pay the price and realize the benefits—are not legally permitted in medicine (1, pp. 341–351). I have in mind, for example, that you cannot contract for less than "standard" medicine. You cannot shop around for "bargain-basement" medicine that fails to reach the accepted standard, however economically feasible or desirable such an arrangement might appear to be. Nor can you, through contract, before the event, release hospitals and physicians from liability for negligent injury arising from substandard care. Nor is it likely that any physician could be held by contract with a patient to achieve a specified therapeutic outcome (2, pp. 253–259). These, I take it, are significant signs from the law itself that contracts, while necessary, are not fully adequate; and are sometimes, indeed, counterproductive as a model for fostering humane and ethical medicine.

Why Contracts Are Needed

Contracts are necessary for a number of reasons; and for these reasons contract law is appealing to many ethically sensitive persons (6). I merely mention, or catalog, some of these reasons in passing. First, the radical imbalance of power between the sick person and the physician in the medical clinic cries out for some redress, an end which contract law envisions to some degree. The "patient's rights" movement, in the wider context of the various consumer and human rights movements, lends impetus to the legal equalizing of power. Contracts tend to specify rights and duties and conditions which can be, if necessary, legally enforced.

This seems appealing, particularly to a culture characterized by radical pluralism. We no longer have (if we ever had) any widespread consensual views of what human beings are, of what the good life is, or of what our duties and privileges toward each other are. Where there are no assumed first principles with reference to such basic matters, putting oneself in the hands of the medical profession can be perceived as a dangerous enterprise.

And indeed it can be. These dangers are the undertow of the great technological advances in medicine in the last half century or so. Because of the powerful, diversified invasive technologies now available to physicians—therapies and procedures that can significantly help catastrophically ill persons, but which can often equally catastrophically hurt them—many patients are not content merely to say "Do something, Doctor," or "Do what you think is best." Contract law seems attractive because it suggests the necessity for joint decision-making; in its nature it opposes unilateral choosing. It invites physicians and patients alike to respect the personal and the professional autonomy of the other, thereby encouraging discussions leading to "informed consent" rather than "blind trust" from patients.

In these ways contract law tends to challenge the traditional authoritarian models of the physician as parent (or as priest) simply doing "what is best for the patient"—a tradition that no doubt encourages patients to become or act like children. Historically, medical paternalism at its best has been a kind of idealized altruism; at its worst it has shown high-handed hubris and arrogance. No doubt this historical reality is a key element in the widespread consumer demand that physicians be legally accountable for what happens in medicine.

Perhaps it should also be emphasized that in the nature of our modern, often urban society—and in the nature of tertiary-care hospitals and other medical institutions serving wide sections of the populace—medical relationships will be essentially between strangers. Physicians taking care of strangers is the norm rather than the exception in much of modern technological medicine. This is another reason contract law is necessary, and is often seen as appealing.

Limits of the Contract Model

For all these and a number of other reasons that might be adduced, contracts are a necessary (and on the surface, appealing) model for understanding legally what is happening in the medical clinic. But they are nevertheless inadequate; they are limited in value. Like most of the legal presences in the medical world, they promise more than they can deliver. Although it is perhaps understandable that a litigious society such as ours turns to the law to try to bring some moral order into the cultural chaos that medicine reflects, we nonetheless need to emphasize and to reiterate that the law cannot finally help us much with the wider and deeper ethical issues. Declaratory judgments in the law give the illusion of making final, precise, and clear rulings. But the fact is that this is an illusion. Law cannot eliminate the ambiguity, contingency, and lack of clarity, precision, certitude, and finality that exists in medicine. The law is too blunt an instrument to help us much in these matters.

In the same way that we need to deflate the public expectation that medicine can become a cure for death, we need also to challenge the popular notion that the active presence of the law as a third party in the clinic will bring us humane and ethical medicine. We must confess the ambiguity, celebrate the contingency, and criticize the insistence on legal certitude, finality, precision, and clarity in medicine. The public expects more than the law can deliver. Upon careful reflection, one might indeed conclude that the least law necessary is the best law possible. But contract law in medicine is necessary.

Yet insofar as medical ethics is concerned, contract law is woefully inadequate in contributing to the creation and support of a humane and ethically sensitive medicine (6, pp. 118–127). Contract law is essentially limited in that it is minimalist in its ethical demands. Self-interested minimalism is the norm in contractual arrangements. It is inadequate also in that the specifics of a contract would always fail to recognize the full scope of open-ended, unpredictable professional ethical duties in a doctor-patient relationship.

The Gift of Presence. Furthermore, as William F. May (6, p. 118) has persuasively argued, the model of contract "suppresses the element of gift in human relationships." And "gift" is an element which, despite its abuse in the history of medicine, is nevertheless central to taking care of patients. While doctors have sometimes engaged in the "conceit of philanthropy" (May's phrase), seeing themselves only as givers, the element of giving and receiving is at the heart of the phenomenon of sick persons and their physicians making themselves present to each other in their common mortality. Being personally present—the "gift of presence"—is a crucial part of humane medicine. And the contract paradigm tends to obscure this dimension of gift which is at the heart of humane relationships of every kind. Hence, May concludes: "The kind of minimalism that a purely contractualist understanding of the professional relationship encourages produces a professional too grudging, too calculating, too lacking in spontaneity, too quickly exhausted to go the second mile with patients along the road of their distress" (6, p. 120).

Finally, contracts (though necessary) are also, as a dominant paradigm, not only inadequate, but in some cases actively counterproductive of ethical sensitivity. For the contract tends to move the ethical question in medical clinics from "what should or should not be done" to "what is proscribed by law; what is required by law; what is permitted, but not prescribed, by law." When physicians stop asking, "What is ethically correct?" and ask instead, "What is the law?" we have suffered a moral loss in the ethos of medicine.

Contract as a model is also potentially counterproductive in that it tends not only toward a lower standard of care, but (paradoxically) it also increases the temptation for doctors to practice "defensive medicine." To protect their own interests, and out of anxiety before the law, doctors can be tempted to do tests and follow procedures not medically necessary or indicated. One might argue indeed that seeing medicine primarily under a contract model has, indirectly, contributed to and exacerbated the so-called malpractice crisis.

A More Compelling Paradigm: Fiduciary Covenant

To summarize: contract law exists; it is necessary and in many ways appealing. It is not adequate, and it is potentially counterproductive as a paradigm for understanding ethics in the medical clinic. Can we do better? Is there another more promising model we can invoke? I think we can do better; and there is a more compelling paradigm.

I want to suggest that the controlling metaphor for envisioning medicine be not contract, but rather covenant, fiduciary covenant. I believe this incorporates the positive values of contract, but goes beyond to correct some of its deficiencies. The fiduciary covenant model describes more accurately what is happening when physicians and sick persons (and the worried well) make themselves personally present to each other in the diagnostic and therapeutic encounter. This model is phenomenologically and descriptively more accurate; and at the same time it holds up an ideal against which current practice can be challenged and judged. This model is historically rooted in the religious traditions of Judaism and Christianity; but I believe its descriptive and normative power does not ultimately depend on theological assumptions. The earliest significant use of this model as a paradigm for medicine is by Paul Ramsey (8). William F. May further elaborates on the covenant metaphor in a 1975 article (9), but his most elaborate use of it is in his *The Physician's Covenant* (6), which elaborates on the significance of image and metaphor in biomedical ethics.

Veatch develops at length a social contract theory that attempts to define a kind of secular paradigm incorporating some of the better features of the religious model of covenant (7).

As the designation implies, the fiduciary covenant model is rooted and grounded in trust. Not the childlike trust which pleads with the kindly parent figure, "Do something, Doctor!" Not the blind trust which abdicates all adult responsibility and acquiesces, "Whatever you think is best, Doctor." Not that kind of abject trust which seems so often to have broken down when we hear complaints that a patient is not "complying with doctor's orders." No—not that kind of trust at all—but a trust that is mutual, that respects the person of the other, that recognizes the needs of the patient for help, and the needs of the doctor to have a patient, with all that that implies for each.

Such a fiduciary covenant, a covenant of trust, is grounded in response to gifts received. First, the physician's response to the gifts made to her by society: the gifts of medical education, of research facilities, of hospitals and clinics, of licensure and the authority to diagnose and prescribe—in short, the gifts of a profession, apart from which medicine could not exist. Covenant is grounded in the physician's response to such gifts. And it is also rooted in the patient's response and need as the physician offers her gift of personal presence, of expert knowledge, of clinical expertise, and of the socially bestowed authority to pursue the health of the patient.

These responses to gift involve the making and keeping of promises, explicit and implied, by both parties. Hence fidelity to the legitimate expectations of the relationship becomes the litmus test of how ethical and humane the relationship is. Such a model recognizes (and articulates) the irreducible interdependence of human beings; it makes short shrift of all forms of high-handed authoritarianism, and of self-sufficient individualism. It becomes a check on heavy medical paternalism, however well-intentioned; and it is a brake against ideological claims that the wishes of the patient should have primacy or be absolute in decision-making. The covenant model insists that unilateral decisions are always ethically faulty, whatever their substance and whatever their consequences. It is a model that requires physician and patient alike to bear the burden of joint decision-making, allowing neither to abandon the other by withdrawing into silence. In all these ways it affirms a high ethical ideal against which concrete cases might be judged or evaluated.

(If physicians had time and interest to read only one book dealing with doctor-patient relationships, I would strongly recommend Jay Katz's *The Silent World of Doctor and Patient* [10].)

Such a paradigm has profound implications for how the personal presence of physicians and patients to each other will be articulated. It is essentially dialogical. It requires not only the "informed consent" of the patient, as that new and (to many physicians) novel idea has been developed in ethics and in law. But it also requires that physicians articulate some of their own anxieties and fears—including the medical uncertainty they have to deal with every day, and their personal medical prejudices as well. Within the confines of distributive justice (considering that a physician's time is a "limited resource in high demand"), and in the context of the individual patient's needs and desires, such an "uncovering" of the "physician's burden" could be a salutary thing. It could indeed open up clogged channels of communication; and perhaps even more significantly, it could help physicians themselves deal with the ambiguities and uncertainties of their daily routine. Traditional justifications for physicians' always appearing "certain" and "in charge" do not hold up persuasively under the scrutiny of the fiduciary covenantal model (10, pp. 165–206).

Trust in such a covenantal relationship is earned and reenforced by the making and keeping of promises, all in response to gift and in the context of need. It is articulated as mutual interdependence by physicians and patients who are personally present to each other in the common pursuit of the intrinsic *telos* or goal of medicine, which is the health of the patient. If the "well-working of the organism as a whole" cannot be achieved, the goal becomes the mutual interdependence of physician and patient in caring for the patient in the disintegrating of the organism. More attention needs to be given to the appropriate *teloi* of medicine—the ends intrinsic to medicine, and integral to its practice (11).

This is the ideal which I believe we should keep before us as we try to go beyond the minimalism of the contract paradigm. Fiduciary covenant paradigmatically captures the complex richness and unpredictability that lie at the heart of humane doctor-patient relationships.

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The Physician's Experience:

Cases and Doubts

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Breast Surgery
Alisan B. Goldfarb

I am pleased to participate here so that I can question in public all the things I normally question in silence. I am going to discuss two patients. Case 1 raises a broad issue that I deal with almost every day during office hours. Case 2 raises many different moral and ethical dilemmas for me as a physician.

Case 1: When Nobody Knows the Right Answer. A 51-year-old woman had a mammogram revealing abnormality, a few calcifications, a subtle change from her previous film two years ago. On biopsy, the change proved to be mostly fibrocystic breast tissue; however, there were several microscopic cells of intraductal carcinoma.

In breast surgery there are lots of choices, depending on the diagnosis. Some of those choices exist because the different medical treatments are equal, and some of those choices exist because we really do not know what is the right treatment, because we have no idea what the natural history of the disease would be. The latter was true of this case: these microscopic clusters of malignant cells indicate a new entity. Because the mammogram machines have become so sophisticated, microscopic abnormalities are found. Left alone, they might never turn into a problem. However, it is difficult for a physician to look at a few malignant cells and believe that.

So the patient came to me for a third opinion. The first opinion had been to do a mastectomy, the second that she should do nothing but careful follow-up. She came to my office not because she wanted a tie-breaking vote, but because she heard that I would take some time and try to educate her about why she had gotten two such disparate opinions.

What I was faced with, of course, and what I am faced with often in this dilemma, is that nobody knows the right answer. Most of our information comes from extrapolation from diseases that are similar, but not the same. Each of us has our own emotional bias. At most meetings of breast surgeons, we end up in hot debate. So, in educating a patient, particularly an intelligent and well-educated patient, do I have to be careful not to lean toward my biases? If my bias is based on what I consider to be a good medical education and many years of experience, should I not be biased?

The other question is, when I am educating the patient, can I be sure that she is understanding what I am telling her? If she chooses what I would feel is the better course of action, and I am not certain that she has understood, do I really have to make her understand? If she is choosing what I do not think is the better course and I do not think she has understood, do I have to make her understand?

If she turns around and says to me, "Dr. Gold-

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farb, what do you think is best? What would you do?" I find the questions unanswerable because it is not me, I do not know what I would do, and I really do not know what is best. I know I have feelings about what I think is best.

Such consultations are tremendously difficult. Generally, when you are giving the third opinion, you cannot say "Well, you could talk to other doctors and see what they say." I saw this patient about two months ago, and she has not yet made up her mind. She has not seen more physicians, but she has consulted other ancillary specialties, including "alternate care" specialists, in trying to make up her mind.

Case 2. When Complex Medical and Psychosocial Developments Intersect. I first met this patient in 1986, when she was 27 years old, and came to me for evaluation of a peculiar thickening in her left breast. She came to my office with her mother who, in fact, had been operated on for breast cancer in 1981. Although this young lady was an adult, and married, the mother did most of the talking at the initial office consultation.

Highly significant in the patient's medical history was that, at age 11, she was treated for Hodgkin's disease, originally diagnosed in a superclavicular node. She underwent extensive study, including staging laparotomy, and radiation therapy to the test area as well as the abdominal area. She was well for several years; then a peculiar enlargement of her tonsils was noted. The Hodgkin's disease had recurred in her tonsil area and she was again treated with radiation. After that, she was entirely well. Between her adolescent years and the present, she did undergo one lymph node biopsy, which was negative.

Either because of her previous illness, or its treatment, or the emotional problems that go along with them, the patient herself was quite frail, both in physique and emotional presentation. The idea of biopsying the breast was something that she went along with and tolerated easily. Unfortunately, it did prove that she had a small malignancy of the breast and although other options seemed perhaps appropriate, the decision was to do a mastectomy. She tolerated the surgery well and the prognostic indicators were favorable. She required no chemotherapy. She and her mother decided that she would like to be followed up by a medical oncologist, and they chose someone who in personality fit their needs. My feeling was that, since she did not require chemotherapy but careful follow-up, the choice was a good one. He was a rather grandfatherly, paternalistic sort. She was carefully followed up.

Then, of course, the question of whether she should become pregnant arose. The issue in my discussing this with her went beyond the breast cancer, because I had her well-meaning but overbearing mother saying to me, "She can barely take care of herself. Tell her she can't tolerate it." I had my own questions about whether a patient with breast cancer should sustain the high levels of hormone stimulation that occur in pregnancy. I also had the real question of whether this patient, who appeared so frail and snapped back physically from an operation so slowly, would deal well with the demands of pregnancy and taking care of a young child. The patient independently decided not to become pregnant, or even to consider pregnancy.

The next thing I knew a letter arrived on my desk from an adoption agency asking me whether this patient was fit medically and emotionally to adopt a child. My questions became complicated. This was the young lady who (and I had breathed a sigh of relief) had decided on her own not to become pregnant. Could I write that emotionally and physically she was a good candidate to adopt a child? Was my responsibility to the patient, who I knew would like to be a parent? To the adoption agency? Or to the child ready for adoption? A complicated problem. The paperwork, of course, churned on and on.

During this patient's follow-up, a thickening in the other breast was noted, which was biopsied and proved to be benign. Unfortunately, our breath of relief was short-lived because soon thereafter a lymph node on the other side was noted to have metastatic breast carcinoma. A second primary lesion was found on the other side, so this patient had to undergo a second mastectomy. Unfortunately, this malignancy was much more aggressive, and chemotherapy was required.

I was concerned that the original choice of the medical oncologist, the grandfatherly type, who was gentle and appropriate in dealing with this patient and who, in fact, had been the one who found the metastatic node in her axilla, was not aggressive enough to give this young woman the complicated treatment that she needed. The radiation therapy had left her with some disability that would make the chemotherapy much more difficult. Luckily, he graciously phoned me before deciding on what treatment to choose, and together we decided for consultation with one of the young, aggressive chemotherapists in the city with whom he said he would be happy to work. This would maintain his relationship with the patient and allow her the more aggressive chemotherapy.

Then the mother came up with more advice. "This is going to be very aggressive treatment, don't you think she should move in with me while she has it?" And the patient, trying to save her marriage, which was in some difficulties, said, "I live in New Jersey. Can't I be treated in New Jersey?" My position then became not breast surgeon, but more advisor–marriage-counselor–psychiatrist.

Another issue was raised in this patient's case. The patient had always experienced some heavy bleeding with her periods, and was known to have a fibroid uterus. Once the difficult chemotherapy was begun, her gynecologist suggested, "Since you will not be having children anyway, and heavy bleeding might be a problem while you're on chemo, let's do a hysterectomy before we begin the chemo." The patient was quite tearful as she reported this information to me. I had great difficulty with this particular issue, because I saw this lovely young lady, who had already lost both breasts, facing the loss of the last of her female organs. Having seen many, many patients through chemotherapy, I felt strongly that her periods would probably end anyway after a cycle or two of chemotherapy. I felt that this advice by her gynecologist was unfeeling. I wrestled with the question of my place in talking with the patient. Should I call the gynecologist? Should I call the medical oncologist and have the medical oncologist call the gynecologist? Or should I speak with the patient, or even her mother, about whether they should insist on a dialogue between gynecologist and oncologist?

Intensive Care Units
Thomas H. Kalb

A recent incident in the medical intensive care unit in which a patient temporarily refused medical treatment highlights for me some practical and frequently encountered issues regarding the patient-physician contract and points up some features of the ICU environment which bring unique ambiguities and new twists to bear on this contract.

A 39-year-old man who works as a hospital administrator (at another institution) and carries the underlying diagnosis of alcohol-related liver failure with cirrhosis in 1990 had a lengthy stay in The Mount Sinai Hospital for complications of cirrhosis, including life-threatening bleeding gastric and esophageal varices, for which he underwent emergency surgery—a distal splenorenal shunt.

His postsurgical course was complicated by the development of progressively tense ascites, a buildup of fluid in the abdominal cavity. To relieve discomfort, a catheter was inserted to drain this fluid. Of note, the ascites was milky, with a relatively elevated triglyceride level, and this analysis, coupled with the temporal relationship to surgery, was consistent with the possibility that abdominal lymphatics had been interrupted at laparotomy, resulting in spillage of lymph fluid into the abdomen—in other words, a surgical complication. It was not clear from the chart record whether this possibility was discussed with the patient, although the patient's fiancee, who described herself as having previously worked as a nurse, assumed with evident displeasure that this was the case. Moreover, the amount of fluid which could be removed safely was limited by the development of renal insufficiency, reflecting the sensitivity of the kidney to shifts in body fluid volume in the setting of cirrhosis.

After nearly three weeks of limited success in dealing with these problems, the patient was discharged on a regimen of fluid restriction and diuretics, with residual though stable ascites and moderate renal insufficiency.

One week after discharge, he was readmitted to the medical service for increasing abdominal girth and lethargy, and on the second hospital day was transferred to the medical intensive care unit for recurrent gastrointestinal bleeding. In consultation with the admitting gastroenterologist, the ICU team—consisting of attending physician, fellow, and medical resident—proceeded to initiate several therapies to stabilize the patient. These therapies included the reinsertion of an abdominal catheter for drainage of ascites. Based on his condition, it was agreed that a relatively small volume of fluid would be drained, and that thereafter, the catheter would be clamped.

The patient was lethargic but easily arousable and oriented, and he was accompanied by his fiancee throughout the evening. The procedure was described to both of them by the medical resident, they agreed to it, and consent forms were signed.

In the evening, the ICU is staffed by a medical resident alone; a backup attending physician and fellow are available on call. When the covering resident returned to the patient's bedside that evening to clamp the abdominal catheter, she was stopped by the patient's fiancee, who insisted that the catheter not be clamped, saying (rather colorfully) that she would prevent all intervention until the attending gastroenterologist was consulted, adding, "I don't know you from Adam." The resident attempted to reexplain the indications, but both patient and fiancee steadfastly refused. The resident contacted the ICU fellow and the ICU attending, but the patient's fiancee refused to come to the phone, stating that she suspected a ruse to leave the patient unattended so that the catheter could be clamped. Observing the ruckus, the nursing staff independently notified the administrative supervisor, who instructed the resident by phone that the catheter not be clamped against the family's wishes, and recommended that the attending gastroenterologist be notified. After two hours, the gastroenterologist contacted the unit, and with a few reassuring words to the fiancee, she finally agreed to continued medical care by the ICU staff. In the interim standoff, nearly three liters of unintended drainage occurred. Fortunately the patient suffered no immediate untoward effects attributable to this incident, although his subsequent course was rocky indeed, culminating one month later in successful liver transplantation. Throughout his stay in the ICU, EG's fiancee never flagged in her vigilance, though as far as I am aware, no further incidents, refusals of care, or other untoward events between family and staff occurred.

When Physicians' Responsibilities Are Shared. Several questions relevant to the patient-physician contract are, in my mind, raised by incidents like this:

- Who is responsible for patient care in an ICU?
- Who do patients and their families think is responsible for their care when they have been transferred to the ICU?
- What are the problems inherent in responsibility shared between ICU attending physicians and staff, and private attending physicians?

Elderly Psychiatric Patients

Bennett P. Leifer

An 86-year-old white man was admitted to the geropsychiatry service for the treatment of an exacerbation of his chronic depression.

Significant in his medical history were non-insulin-dependent diabetes, chronic renal insufficiency, Parkinson's disease, ischemic heart disease, and benign prostatic hyperplasia. Significant in his psychiatric history were previous episodes of depression successfully treated with electroconvulsive therapy.

The patient was a retired engineer, married to a psychiatrist for about 60 years. He and his wife lived on the Upper East Side of Manhattan and always enjoyed the diverse cultural life of the city. His wife had been diagnosed as having dementia of the Alzheimer's type five years before. She lived in their apartment with 24-hour supervision. They had no children and had outlived all immediate family. They did, however, have a close circle of friends, all in their late 70's. Before the patient's wife developed dementia, she and he had been active in their community.

The patient progressively deteriorated during his stay on the psychiatric unit. Not only was he unresponsive to electroconvulsive treatments; he also could not tolerate psychotropic medication because of adverse side effects. His depression persisted and he began to show evidence of an underlying dementia as well as intermittent periods of delirium. There were numerous episodes of dehydration as his oral intake decreased. These episodes would exacerbate his renal insufficiency and he would become more delirious or obtunded. Intermittent intravenous hydration would result in periods of greater coherence and orientation. However, hydration had to be monitored closely because of the risk of congestive heart failure.

In his fifth month of hospitalization his close friends brought in a copy of a living will he had completed prior to his hospitalization. During a period of lucidity, when he was deemed to have capacity for medical decision-making, he reaffirmed the items enumerated in the living will, specifically that in the event he faced a hopeless prognosis, no cardiopulmonary resuscitation, no intubation, no dialysis, no antibiotics, and no tube feedings be done.

At one point, he participated in his own discharge planning and agreed to go to a nursing home rather than return home. He felt that the burden of his medical and psychiatric care combined with his wife's custodial home care could not be provided effectively in their small apartment. He adamantly did not want his wife to go to a nursing home because her situation was stable with a home health aide in their apartment.

Two weeks prior to his scheduled discharge to a nursing home, he experienced a myocardial infarction and was transferred to an acute-care medical unit. Cardiac evaluation subsequently revealed that he had severe congestive heart failure and end-stage ischemic cardiomyopathy. He lapsed into a stuporous state, unresponsive to supplemental oxygen and diuretic therapy. He did not eat, required total nursing care, and only occasionally opened his eyes in response to his name.

Both medical and nursing staff expressed concern about whether an acute-care hospital unit was the appropriate place for him in light of his poor prognosis and because no acute medical care was being provided. The nursing home that had previously accepted him now refused him admission, stating that his medical condition was not stable enough for him to be transferred at that time. His friends visited often, repeatedly stating that a vegetative state was precisely the situation he had wished to avoid by writing his living will. His wishes, as outlined in his living will, were respected, and no tube feedings or parenteral nutrition were initiated. He died ten days later of intractable congestive heart failure.

Questions Posed by Living Wills and Advance Directives. This case highlights some of the key questions concerning the doctor-patient relationship. Physicians and caregivers often find it easy to go along with patients' and families' wishes when they conform to their own. In contrast, they become resistant and uncomfortable when these wishes diverge from what caregivers think is reasonable or clash with caregivers' own values.

Once a physician enters into discussions of advance directives with a patient, does this commit the physicians to actively perform the patient's advance directives? Does it ensure others' compliance? For instance, in this case, is it the physician's responsibility to withhold food and parenteral nutrition from the patient? What would have been the physician's responsibility if, during one of the patient's lucid moments, he expressed his view that his intractable depression had become unbearable and that he wanted assistance in ending his life? How should a physician assess a patient's decision-making capacity when he or she is suffering from a psychiatric illness? As obtaining advance directives becomes a standard legal and a standard procedural part of the doctor-patient relationship, physicians and caregivers must gain a greater understanding not only of what these directives mean to patients, but also of the responsibilities and obligations these directives entail.

Child Patients

Audrey Schwersenz

The doctor-patient relationship has changed quite a bit from the days of the omnipotent and omniscient Ben Casey. Decades ago, living will and do-not-resuscitate orders were barely discussed; many patients, perhaps most, quietly waited for their physicians to make personal and important decisions for them. Whatever has heightened patients' awareness of their own rights and autonomy, whether it be better education, more liberal politics, or the ubiquitous malpractice lawyer, it has changed the way medicine is practiced today.

The child patient, however, is a minor who is usually not allowed self-determination of his or her medical needs. A pediatrician is often placed in the role of surrogate for the young patient when a parent is absent or unfit. I am a pediatric GI fellow who has been working in Mount Sinai's liver transplant program for almost two years, and I was recently involved in a case in which the doctors and not the patient were responsible for determining whether a child was going to have any future at all.

A 12-year-old boy was referred to my service for a liver transplant in 1990. He had been born with extrahepatic biliary atresia which was successfully treated with a Kasai operation in infancy. About a year before we at the service met him, he developed progressive jaundice, ascites, coagulopathy, fatigue, and hypersplenism secondary to cirrhosis.

The nonmedical issues in his case were less straightforward. He had a history of developmental delay and learning disability requiring special education. A year before, his stepfather was killed in street violence. The child became truant and difficult to handle, and he did not fare better when he was moved down south to live with his grandmother. Eventually he returned to New York, where he was placed in a group home for children with behavioral problems and other disabilities. His mother continued to maintain close contact with him, and the ultimate plan was for him to return home.

He was admitted for a pretransplant evaluation that lasted over a week. I found him to be a soft-spoken, good-natured boy who had difficulty expressing himself verbally in an intelligible way. Our studies were extensive and required multiple invasive and noninvasive procedures and medical consultations, which he tolerated without complaints. Psychological testing and evaluation are part of the study, and our child psychologist felt that he was a good candidate for transplantation.

Our evaluation required that he have a CT scan. Orders were that he take nothing by mouth overnight, and the scan was delayed until the afternoon. In the radiology suite there were further delays. He complained that he was hungry and then left the procedure. He was eventually brought back by security. My guess is that he was just going to the cafeteria. Nevertheless, Mount Sinai requires that such a patient be observed one-to-one and receive an emergency psychiatric consultation. The psychiatrist saw the boy in his most stressed state and documented that his impulsive behavior and borderline mental retardation made him a poor risk for a transplant.

I now had two trained psychiatric professionals with opposing opinions regarding the boy's candidacy. I called his group home in order to get a third opinion from a psychiatrist who had known him for over a year. She told me that he was not mentally retarded, but that he did have an impulse-control disorder and expressive-language disability. I also spoke to his pediatrician, who confirmed that he was very cooperative except when he was hungry. I had no trouble sympathizing.

I had to present the boy's case to our recipient review committee to establish whether or not he was a candidate. I reviewed the facts of the case for and against transplantation.

FOR:

- a transplant was medically indicated
- he wanted one, and his mother showed no ambivalence
- he was not profoundly retarded; in fact his disabilities could be attributable to chronic liver disease
- being a child, his future was totally unpredictable

AGAINST:

- he had an unstable home environment
- there was no way to be sure whether he could ever take responsibility for himself
- his impulsive behavior might make it impossible for us to provide adequate care either in the hospital or at home

To be honest, I never created such a formal list. In the end, my own opinion was shaped less by those facts and more by my instinctive feelings about the boy based on my many interactions with him.

As objective as the recipient review committee aims to be, the influence of the way in which the patient's case is presented cannot be underestimated. There were no rules that said I had to present all the reports of the various psychiatrists and psychologists. I knew that it might hurt the child's chances of acceptance to discuss the views of the emergency consultant in particular. But my own ethical beliefs led me to present all the opposing views as fairly as possible, and I asked that all people involved in the case be present to represent themselves at the meeting. Needless to say, there was much hesitance to list him as a candidate for transplant.

The debate continued for several weeks, and the decision was continually postponed. I was vocal about my own opinions. For example, I asked the committee whether a reformed alcoholic is more likely to be compliant than a child with a learning disability. Why not consider the boy more compliant than most, especially since he lived in a structured group home? Should potential compliance be used as a criterion for child recipients, since we should expect total noncompliance during that awful period of time known as adolescence?

I encouraged everyone to meet with and speak to the boy before coming to a conclusion. In the end, he "won" himself a transplant by charming Dr. Miller with his good nature and his capacity for sophisticated analogy. He compared his transplanted liver to a race car engine, and understood that maintaining his liver would also require frequent check-ups, many tests, and tune-ups and taking medicines every day (actually, comparing cyclosporine to motor oil isn't that far off). He eventually did receive a transplantation and—luckily—he was a model patient. We have not withheld any meals since his second postoperative day, and he has happily gained a whopping 40 lbs. since the surgery.

The Child's Physician: Protective, Parental, (Occasionally) a Pushover. My discussion here is not on the ethics of transplantation, but rather on my role as physician to my patient. I think that the doctor-patient relationship in pediatrics is unique. My motivation to advocate for the boy's transplant was in part instinctive. Pediatrics allows you to have those instinctive feelings and close interactions with patients. You would not feel uncomfortable hugging a child, or playing with a child, or even acting somewhat childlike, if it allowed you to communicate better, even though these actions might be considered unprofessional in adult medicine. Emotional distance is harder to maintain with a needy and affectionate toddler. It's harder to hate in pediatrics, since the children are usually innocent bystanders, or occasionally victims, of their parents' brutality, irresponsibility or self-destructive behavior. In the end, you lose some of your objectivity, but never your empathy. If being a pediatrician could be summed up in just three words, they would be: protective, parental, and (occasionally) a pushover.

My responsibility as a child's doctor is to advocate for him or her what would be the best course of action medically, keeping in mind issues of quality of life. This is often colored by the patient's and parents' desires and, rarely, by my own moral instincts. In choosing a treatment plan, I do not believe that it is my role to determine what the burdens to society are, either financially or socially, and I gladly relinquish that responsibility to the ethicists.

The Doctor-Patient Relationship:

Panel Discussion

Moderator: Rosamond Rhodes, Ph.D.

Rosamond Rhodes: Let me briefly review where we are at this point. Four philosophers and one physician outline their views of what the doctor-patient relationship actually is. Prof. Bernard Baumrin argues that the doctor-patient relationship should appropriately be seen in terms of a consumer contract, like buying tuna fish in the supermarket. Prof. John Ladd has argued for the ethics of virtue, where we take seriously our responsibility of other-regardingness. Prof. White argues for adopting a view of the doctor-patient relationship in terms of a fiduciary contract that pays a lot of attention to trust and promise. Dr. Daniel A. Moros argues for a view of the doctor as the trusted advisor to the patient, who is required to use rationality and knowledge of science in doing the right thing. And Prof. Laurence McCullough argues for seeing the problem of the doctor's role in terms of finding the middle ground between the duties of self-sacrifice and legitimate self-interest. Then four physicians present cases. Do the theoretical approaches help us answer the questions raised by the doctors about what they ought to do?

To begin, I ask Dr. Aufses, Ruth Ravich, and Dr. Gorlin if they have any comments.

Arthur H. Aufses Jr. Speaking not as a surgeon, but as a patient who had his first operation at The Mount Sinai Hospital in 1930, I do remember something about it, but I don't know what the contractual relationship between the surgeon and my father was. They were colleagues, since my father was a surgeon here. I do remember very clearly having been operated on again at Mount Sinai Hospital in 1943. I do remember that at that time, there were no such things as consent forms. If you were admitted to the hospital as a patient and your doctor was a surgeon, it was assumed that you were going to have an operation, and you went ahead and had that operation, and you either did well or you didn't do well. Dr. Baumrin says that most contracts are implicit; many are promises; and only a few are written. And in those days, none of them were written. But then he says, the patient is a purchaser of services, the doctor is an offerer. That really stuck in my craw, and I asked myself, how did we get from point A, 1930, 1943, no written contracts, to point B, where everybody is an adversary of everybody else? And clearly I think the answer lies in a multitude of factors. I think the patients are in part responsible. I have no doubt that the medical profession itself is responsible in part. And I also think that there are outside forces, third parties—insurance companies, and lawyers—leading to this change in the societal view of the doctor-patient relationship.

Rhodes: Aside from being a model patient, Dr. Aufses is also our chairman of surgery. Did you have any questions that you wanted to ask of any of the speakers?

Aufses: Dr. Goldfarb raised some interesting questions. She asked whether doctors should use their own biases and whether patients understand that bias comes into play. I would say that physicians, but especially surgeons, always use biases in one way or another, although we try to keep them under wraps as much as we can. And I think all of us who deal with patients would agree with you that patients only understand, or only hear, what they want to hear. And by and large, they do not want to hear things that they don't

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want to hear, and they don't understand. It is to your credit that in dealing with your patients you enable them to understand what you're saying. But how do you know if a patient understands what you're saying?

Alisan Goldfarb: I can't simply use the fact that they came to the same conclusion that I did as evidence that they understood. Many patients will clearly ask questions that signal that they understand. Many, in fact, come with journal articles with notations on the side, and they ask sophisticated questions. And yet sometimes it is clear to me that, although they are saying the right words, they haven't put together some of the pieces. That sensitivity may only come with years of seeing patients. And that is where my moral dilemma comes in. Can I trust my biases—can I say to myself, my bias comes from experience? Or are my biases a reflection of other baggage that comes with me as an individual? It's clear to me that my colleagues who go to the same meetings and read the same journal articles sometimes come to different conclusions. As physicians, making decisions for individual patients, are we dealing with them as individuals, or are we dealing with them as members of a group? Have we brought into the account the patient's personality? Particularly in what I do, there are many decisions that may not be medically ideal, and yet are correct for a particular patient. How much time does a physician devote to a patient to try to figure out what is right for an individual?

John Ladd: "Bias" is a dirty word and so I think you are downgrading what you're doing by calling it making use of your "bias." I think that to make a judgment, which might be called a value judgment or assessment, on the knowledge that you have, is not bias.

Aufses: There's an expression that good judgment comes from bad experiences, which come from bad judgment.

W. D. White: I think your analysis of this is astute, and worth reexamining. The issues you're dealing with, particularly in breast cancer, are complicated. There are the communication problems, and the disagreement amongst the experts about what is optimal treatment, the costs and benefits of the various options, and the fact that the options clearly relate to nonmedical factors like lifestyles and the values of the woman involved. There are also the paradigms which physicians bring to problems rooted in their histories and their experiences. These elements go far beyond any formal declarations of the informed-consent rules. They take you toward the establishment of a humane medicine. And that is essentially the direction of the Jay Katz analysis in *The Silent World of Doctor and Patient,* a book that I recommend.

Laurence McCullough: I think we can say something about what it means to understand. And actually it points to an interesting research agenda in clinical medicine. Some people are distinguishing two kinds of understanding. One is cognitive—I've got to know what my problem is, I've got to know what will happen if you don't do anything for me. And I have to have some sense of what might happen if you do this or that. It's the notion that I have certain possibilities and I can trace their implications reliably into the future. That kind of understanding is a kind of a mastery of information. The other, which is often overlooked, is evaluative understanding.

Of these alternatives that you present to me as the patient, say, to manage breast cancer, which one makes the most sense in terms of what's important to me for my health, how I want to appear to others, my relationship with my husband, others, and the like? All of that has to be taken into account.

Since the informed-consent process only regulates what physicians are obligated to do, in other words, to give information, it hasn't looked at the other side, at what the patients have to do. They've got to cognitively and evaluatively understand, and they need help.

The assumption is that we can just do this routinely, but we can't. These are very complicated pieces of information. Simple things, like asking the patient, "What's important to you in managing your breast cancer?" and getting the patient to say, out loud for herself, maybe for the first time, what that would be, sets a basis for some of these discussions. It's not as mysterious as it's been left. Appreciating the complexity opens up a whole research agenda. What would cognitive understanding be? What would clinically count to show it has occurred? What is evaluative understanding? What would count clinically as that occurring? These are empirical questions we could answer.

Daniel A. Moros: To go back to my own concern, the role of the physician as an applied scientist, and the difficulty of applying science to human life, I thought that Dr. Goldfarb illustrated what a struggle that is, because there were things she definitely knew, and things that she was less certain about, and then she was also confronting the ambiguity of applying this sometimes more and sometimes less certain knowledge to an individual patient.

She made an intriguing comment about what she might have done differently. I believe this process of searching through one's experience, and critically evaluating oneself, is a central feature of good applied science and good applied ethics. I wonder, Dr. Goldfarb, would you do the same thing again? Do you think, in retrospect, that your own conclusions were correct?

Goldfarb: Would I have done the same thing had I the opportunity? I have, unfortunately, had a similar patient since. I treated her differently. And I unfortunately had the bitter pill to swallow. After I made my suggestion she sought care with another physician.

White: But the burden of joint rather than unilateral decision-making is the real issue here, isn't it?

Goldfarb: I think that by the nature of my practice, there is no question but that all decision-making is shared. The only decision that is not shared is that every abnormality gets a biopsy. Once we have biopsy information, then what to do with that information is always shared. I have been in practice for 11 years, and in all those 11 years only two patients have sat across my desk and said, with a straight face, "Whatever you say, doctor."

Richard Gorlin: One of the issues I am concerned with is the tension between physician paternalism and patient autonomy. If you are going to participate as a patient advocate, you have to take on a certain paternalistic role. You have to do so to some degree, because otherwise, you're going to sit there and simply say to the patient, here are the four options. I'll present them to you as best I can. I'll give you an objective evaluation of the data as best I can. It's a Chinese menu, you pick. And in some sense, this approach meets a certain obligation. But as somebody who presumably understands the patient, a physician has a role as a counselor, an advisor, an advocate. All of this depends on your assessment of the person's ability to understand. How about the many patients who don't have that comprehension because of borderline mental status or a language barrier that's difficult to get past? Then there's the issue of the snapshot: you see a patient who is called on to make life-threatening or life-transforming decisions—how often is that done at a single session? Do you tell the patient that this is the big one? One of my cases might involve heart surgery. Should the person have that operation or not? Should the individual have a week for contemplation and a chance to assess the options? What is it I really want to work out with them? How does hostility toward a patient bias the interaction or impair the decision-making process? That has always concerned me. It can almost be punitive.

Rhodes: I have a question for all of you. The issue came up particularly in Dr. Kalb's and Dr. Goldfarb's case. In Dr. Kalb's case there is an attending physician, and there are also the physicians working in the ICU. And in Dr. Goldfarb's case, there was the gynecologist who wanted to do a procedure that Dr. Goldfarb thought was inappropriate. When another physician is doing something inappropriate, or when you're involved in a situation of multiple physicians working together on a case, who is the doctor for the patient? What is the relationship of these many doctors to the patients?

Thomas H. Kalb: In my experience, each case provides its own answer. And the process that occurs in the intensive care unit and in a lot of medical settings is not dissimilar to the process that was described in the pretransplant meetings, in that different professionals advocate different positions. Decisions are made by force of science, by the force of persuasion, and by the individual nuances of the case. According to the ICU model, an attending physician in the ICU is functionally running the show. However, the ICU attending has to deal with institutional regulations and the reality of the fact that each patient has an admitting attending physician, and that a balance comes into play with each patient that depends on that individual physician. Sometimes this is all explicitly stated and sometimes it's only implicit.

Ruth Ravich: Patients are not told about the rules of the hospital, so they don't know what they need to understand. For example, when a patient goes into the ICU, the attending physician should explain the rules to the patient and the family. It needs to be said that theoretically I'm still your doctor, but what's going to happen is going to happen there, and I'm not the person who is going to be consulted about it. We really don't pay enough attention to telling the patients the formal rules and the informal rules. And in this case, there's a difference between the formal rule and the informal rule, and it makes it even more difficult.

Rhodes: Dr. Kalb, let me make my question a bit more pointed. The patient is always your patient, you're always the doctor. Is it ever appropriate for doctors to disagree, to challenge the primary attending?

Kalb: That's the way it always happens. That's the norm.

Rhodes: Do you let the patients know that you disagree?

Gorlin: That is exactly what I wanted to get to.

There has to be an accountable primary physician. That responsibility can move around. But then it ought to be explicitly stated by the primary physician to the patient, that the baton has been passed to another individual who becomes the primary advocate of the patient. I believe that one of the greatest sources of discontent and confusion for the patient is when each successive consultant comes in and says, "Well, I think you ought to do this" instead of saying, "I will talk with your doctor, and we will arrive at a final recommendation that will be presented to you for discussion." I think that as physicians we often fail in this responsibility. There is always the temptation to act as number one.

Kalb: In the case that I described, I think the transfer had been made along with that statement. There was an explicit understanding that authority had shifted, and, in fact, the patient was in a different room, had met different doctors, had spoken with them. But when push came to shove, in this particular case, the transfer of authority broke down on an emotional level. So you're right. What the patient believes and what the doctors are doing in performing their duties in dealing with the ambiguities involved in a case are two different things. And I agree they should be considered as discrete and separate.

Ladd: I have only one remark, and that not as a philosopher but as a past patient. I was in the hospital a few years ago. You sit in the hospital—and I'm a fairly intelligent person, and they know I'm a professor, but these guys come in and start telling me, "I'm Dr. So-and-So, and you're going to go in to such-and-such tomorrow." And then five minutes later somebody else comes in and says, "I'm Dr. So-and-So, and this is going to happen to you." After a while, I said to my own doctor, "Who is this and that Doctor So-and-So?" He said, "He's not a doctor at all, he's a medical student. And that is somebody who's just helping us out." What happens is that, as a patient, you don't know what's going on. You don't know who's in charge and what's going to happen. And I think this is purely a matter of hospital mores which could easily be solved just by telling people what's going on.

Aufses: Well, I think it's a lot easier to deal with this particular problem on a surgical service, because not only ethically but legally, the individual who contracts to do the surgery is responsible.

McCullough: May I talk out of school? I'm not going to describe your institution, but one in which I work in Houston, which has an open adult ICU. These problems arise all the time. Perhaps the attending of record can't be reached. Now if I'm the family physician and I were to send Ms. Ravich to Dr. Aufses, I would not be in charge of the surgery. Dr. Aufses would be in charge of the surgery. And I would not presume to tell him how to practice his specialty. Yet the presumption is often that the generalist or someone from another subspecialty can tell the critical-care physicians how to practice their particular specialty.

I asked my physician colleagues, why is your ICU open? The bottom line is money. The attending physicians of record refused to let the ICU become a closed ICU, because they priced out the impact on their billings for the patients, and they didn't like what they saw. It seems to me that patients should understand that a particular policy is driven by what I think should be labelled as mere economic self-interest on the part of physicians.

Bernard Baumrin: I want to go back to tuna fish. Go with me, for just a moment, a thousand years into the future, when instead of our present massive ignorance we've actually got almost everything figured out. In that kind of world, assuming there still are physicians and you went to one with a complaint, the physician would simply say, "That's wrong, and the way to fix that is such-and-such." And if the patient said, "Well, no, I don't want to fix it that way," the physician would simply throw the patient out. There wouldn't be an issue any more. Having the knowledge, the physician would then address himself or herself to fixing the thing up with that knowledge. If someone wanted to substitute their knowledge for physician knowledge, the physician would just tell them, "Go home and do it yourself, because I'm not going to assist in applying nonscience to something that has a scientific solution."

Back to tuna fish for a moment. What I was suggesting is, the patient comes to buy something which is, they hope, just like a can of tuna fish. Some day, we hope, getting medical treatment will be like buying a can of tuna fish. And when it is, informed consent will be irrelevant; patient autonomy will be irrelevant; hearts and flowers, warmth and feeling, all this stuff will be totally irrelevant. But in our present state of ignorance, which is, after all, a lot better than it used to be, we still have need of these things. I don't want to be cruel and stupid and insensitive, but it's just bedside manner. It's nice to befriend patients, to help them through difficult periods, to help them make decisions about the future disposition of their affairs and the various kinds of therapies that might be employed. But if we really knew exactly what would work, they wouldn't be participating in the decisions and it wouldn't really matter how warm or friendly or kind or well-meaning the physician was.

Aufses: Dr. Rhodes, you asked the question about what happens when doctors disagree, and should patients know that? And Ms. Ravich whispered the answer right away: "Patients always know it." It's clear, and Dr. Goldfarb gave you the example. The patient came to her for a second opinion or a third opinion, and then goes for another opinion. Patients know that doctors disagree.

Prof. Baumrin went a thousand years ahead. I would go in the other direction. All you have to do is go back to 1905, and from 1905 to 1960. Every doctor in the world knew that the only treatment for breast cancer was radical mastectomy. That was it, there was no other treatment. You could give the patient radiotherapy, but the treatment was radical mastectomy. And one of the problems that the breast surgeons now face is, they're doing lesser and lesser operations, and rightly so, they're beginning to ask themselves questions. Are we going too far in the other direction? And is this what medicine is all about? We're not an exact science. We can cure appendicitis. We can take out the appendix and nobody gets appendicitis again. But a lot of other things are in a fairly gray zone. And I think that when Dr. Goldfarb asks whether she did the right thing, the answer is of course she did, at that moment in time. But there may be a different answer tomorrow.

Moros: I want to address comments to Dr. McCullough and Dr. Ladd because their previous comments go to the heart of what I feel has become an increasingly powerful misconceptualization of what medicine is, and this misconceptualization produces negative results. Dr. McCullough suggests that the structure of ICU practice is a reflection of financial interests. I grant that there may be some truth to that. But we have a complex, modern, somewhat scientific system that still runs by rules and traditions that are one, two, and three hundred years old, including the original division of subspecialties and the structure of medical training. I see no sign that all of the work of medical ethicists, all of the involvement of legislatures and advocacy groups, has in any way addressed any of the problems of the inherent disorganization of medical care. In fact, I think they've been slowly making it worse.

Let me offer an illustration to support my statement. Everybody here agrees that doctors should talk to patients. For the last twenty years, since I started in medical school, I have been hearing that we are going to shift resources to primary care, that we are going to pay doctors more to talk to patients, and that we're going to get doctors who talk to patients. But I know very well that today, we pay a smaller percentage of the medical budget for talking to patients, and for caring for patients directly, than we did twenty years ago.

So all the involvement of additional parties trying to rationalize and modernize the structure of medicine has failed. I'm concerned that sometimes doctors protect a financial prerogative, for example by the way the ICU is structured. But I'm more concerned about the fact that everybody else who has gotten involved in restructuring medicine may actually have made it worse.

McCullough: The history of funding medical care gives a different picture. The present structure reflects how Medicare and Medicare's payment schedule has influenced the private paying schedule. Medicare was created to provide health care for all older Americans. But that's not the reality. To get the bill passed, President Johnson sat down with the American Medical Association and the American Dental Association and the American Hospital Association and said, What do you want? The American Dental Association said, "Leave us alone." And he said, "Fine." The AMA and the AHA said, "We want to be in control." He said, "You have a deal. I'll give you a hospital-based, physician-controlled reimbursement system."

What do hospitals do to generate the revenue? They do procedures. They don't do outpatient primary care, talking to patients kinds of things. And that dominant payment scheme, one could argue, has had a much larger historical influence.

Moros: If I told patients that I wanted to bill them for talking to me over the phone for thirty minutes, they would think I was crazy. So it's not just the doctors who have developed this attitude that you get paid only for specifically doing something. It's a pervasive attitude throughout our society. It's true that doctors are guilty of it as well, but it doesn't reside solely with the AMA.

I think even Professor Ladd's comment about his experience of lost control in the hospital reflects some misreading of the medical enterprise. The same thing happens if you go into a law office or if you try to deal with construction engineers. Whenever you have to place your vital interests in the hands of people with specialized knowledge, where you don't have the time or energy to acquire that specialized knowledge, you lose a tremendous amount of control, which can be very distressing. I can see no way to avoid it, although

I can see ways to ameliorate it. I certainly think we all should be sensitive to what patients are forced to experience.

Ladd: I rise to my defense on this matter. First, I didn't want to know everything about my heart, I wanted to know when I was going to go into the operating room. And that's not a matter of expertise, that's a matter of either responding, "I don't know," or else somebody telling somebody else. But to get five different answers within an hour from people who purport to be doctors, who I know are not doctors, is what I have in mind. Now that doesn't really have anything to do with the larger issue that you mentioned.

Rhodes: Going back to Dr. Leifer's case (and I should point out that Dr. Leifer is one of Prof. Ladd's former students), Dr. Leifer raised the question of whether it is the doctor's responsibility to assess the patient's mental status and ability to make a judgment about their own care.

Leifer: The practice of medicine involves the day-to-day, minute-by-minute assessment of patients' capacities to decide about the appropriateness of their care. We reflexively monitor what we think of the decisions they are making. Is it in keeping with their own set of values? It's an issue to be stressed, especially at the end of life. As Dr. Goldfarb said, the doctor-patient relationship requires the doctor to make sure that patients understand and are making decisions consistent with their own values.

Goldfarb: Luckily, I don't have to deal with end-of-life decisions. But I'm dealing with patients making other decisions all of the time. I'm often faced with the issue that a competent patient with the capacity to make a choice who is clearly a rational individual in all aspects of life is making what is clearly an irrational, baseless decision. I can think of reasons why they came to the irrational decision. Perhaps they are thinking only of the present and not the future, or something else may be going on in their life, or they fear a needle stick. Clearly, a psychiatrist is not going to help me. Any psychiatric evaluation is going to tell me that this is a competent, sane person who is in a position to make all the decisions, and yet I clearly see an irrational decision being made.

McCullough: Dr. Goldfarb, do you tell patients that—that they've made an irrational decision?

Goldfarb: Yes.

McCullough: And how have they responded?

Goldfarb: Some of them say, "Yes, I know it's irrational, but it's what I have to do." And some of them tell me that I just don't understand them.

Rhodes: I have just one more question. In other cases that have been described here, the doctor seems have an obligation to the institution. Is there a strict obligation only to the patients? In Dr. Schwersenz's case, does she have an obligation to the committee, or only to her patients?

McCullough: It sound like she assumed that the old motto, my patient comes first, is no longer the sole story, that other parties can be affected by what you do to and for your patients. In any transplant of a scarce organ, where one person gets it and someone else dies, you're not only allocating the chance to survive, you're allocating death at the same time. I don't see how one could, in those circumstances, realistically say, with any faithfulness to the moral world in which you're operating at that moment, "My patient comes first." It sounds like Dr. Schwersenz was very well aware that others must be taken into account equally as well as this child, and thus she was objective. That is, she presented the evidence that she had gathered, then forcefully advocated for this particular patient.

Baumrin: She was a member of the committee, and she had a duty to her colleagues to present the information. On the other hand, she could certainly have attacked the information as unfounded or not well evidenced, and whatever else it might have been. Nevertheless, I would have advised her to manipulate the committee as well as she could have in her patient's best interest.

Gorlin: I think the physician is on a slippery slope by ever being something beyond the patient's advocate-counselor. And that, I think, is the value of the types of committees that you're describing. This person should in fact be excused as other than a presenter of the case.

Aufses: You forgot one little piece. Dr. Schwersenz said that the final decision was made when Dr. Miller was persuaded that this young man was an appropriate candidate. There is a committee of about 55 members. But when the chips fell—going back to our discussion about who's in charge in an ICU—the decision was made by the person who has to do the transplant.

2. Transplantation

The Organ-Tissue Donation Process

Angelina Korsun, R.N., M.S.N., M.P.A.

No matter how effective techniques are for preservation of organs and tissues, surgery, and drugs, the success of transplantation depends on the availability of organs and tissues. The history of transplantation is long (Table 1), but the greatest strides have been made in the last 25 years.

Only in the last few decades has organ and tissue transplantation emerged as a successful and clinically applicable therapy. As transplantation expanded, the procurement process became an increasingly important component. Thousands of people require transplantation. At present, 266 transplant centers throughout the country perform kidney, liver, heart, pancreas, heart-lung, lung, and bone marrow transplants and many more perform corneal, bone, and tissue transplants.

Renal transplant has the longest history of the solid-organ transplants. Well over 80,000 kidney allografts have been performed in the last 25 years. Extrarenal transplantation came into the forefront in the 1980s, although a significant number of patients were transplanted earlier. Initial survival numbers were poor, but pioneers in transplantation continued to perfect the procedures. With the introduction of cyclosporine, a potent antirejection agent, graft survival improved markedly and transplantation became more routine.

Survival rates for most transplants are in the range of 75% and up. For many organs, it is routine to see survival statistics in the 85%–90% range.

Legislation

Significant legislation has been passed over the years to promote and support organ and tissue donation. Some of these legislative highlights are:

1968	The Uniform Anatomical Gift Act (adopted in all 50 states)
1972	PL 92-603, Medicare ESRD Network
1978	The Uniform Brain Death Act
1980	Uniform Determination of Death Act
1984	The National Organ Transplant Act (PL 98-507): established Organ Procurement and Transplant Network (OPTN); established task force on organ transplantation; prohibited purchase or sale of organs or tissues
1986	PL 99-509, The Omnibus Budget Act (OBRA), was the beginning of federal required-request legislation: mandates working relationship with OPO in all hospitals receiving Medicare/Medicaid reimbursement; mandates required request; mandates participation with OPTN
1986	State-initiated required-request acts (NYS 1986)

In New York State, as in other states, a required-request law mandates that each hospital have a mechanism for identifying potential donors and referring them to the appropriate procurement agency. In addition, such a procedure is required by Medicare as a prerequisite for reimbursement. In fact government is quite supportive of transplantation. The Medicare-supported End-Stage Renal Disease network was created in the 1960s, and Medicare now covers heart and liver transplants in certain centers.

To put the magnitude of the donation problem into perspective: in January 1992 24,928 patients were waiting for solid organs, a significant

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TABLE 1
Historical Highlights

1682	First reported bone transplant, Meekren
1881	First reported skin transplant
1905	Introduction of corneal transplantation, Zirm
1938	Isolated organ perfusion, Carrel and Lindbergh
1943	Hemodialysis machine developed, Kolff
1954	First successful kidney transplant in US, Murray
1962	First successful cadaveric kidney transplant
1963	First successful liver transplant, Starzl First successful lung transplant, Hardy
1967	First successful pancreas homograft, Lillehel First successful heart transplant, Barnard
1969	Establishment of first network for organ distribution, South Eastern Organ Procurement Foundation (SEOPF)
1980	Introduction of cyclosporin
1981	First successful heart-lung transplant, Reitz
1977	United Network of Organ Sharing (UNOS) first established as result of requests from non-SEOPF member centers
1984	Incorporation of UNOS
1988	Clinical use of Belzer's solution for organ preservation

Adapted from ref. 1.

increase over the 13,766 waiting in February 1988 (Table 2). These totals do not reflect the additional patients who may have been seeking a bone marrow match, a corneal transplant, or skin and bone transplants. The number of patients on waiting lists has increased by 100% in the past 4 years, according to UNOS.

The unfortunate reality is that a large number of patients on waiting lists still die for lack of an organ or a tissue match. Reported deaths of patients on the solid-organ waiting list registered with UNOS (all organs—kidney, liver, pancreas, heart, heart-lung, lung) (4) were:

1988	1537
1989	1732
1990	2080

These totals do not include patients who have died for lack of an appropriate bone-marrow match.

The problem is not the lack of possible but of actual donors. The number of cadaver donors in 1990 was 4,320; the approximate number of deaths in this country is 2.2 mil/year; potential organ donors are estimated by many experts at 14,000 (4). Over the past four years, the number of donors has remained fairly steady at about 4,000.

TABLE 2
United Network of Organ Sharing National Patient Waiting List, Cadaver Organs Only

Organ awaited	2/1988	1/22/1992
Kidney	12,259	19,548
Liver	473	1,640
Pancreas	86	608
Heart	769	2,291
Heart-lung	159	154
Lung	17	687
TOTAL	13,766	24,928
Transplants (cadaver and living related donor) performed in 1991:	12,669	

Adapted from ref. 2.

The United Network for Organ Sharing

The United Network for Organ Sharing (UNOS) was established in 1986. It is a voluntary, nonprofit group federally mandated by the Organ Procurement Transplant Network to supervise sharing, matching, and distribution of donor organs. UNOS member hospitals are reimbursed under Medicare and Medicaid. UNOS' main function is equitable organ distribution and maintaining statistics on transplantation in the United States. It uses single national lists of potential recipients who are listed in order of point score. Point allocation for kidneys is based on local listing, time waiting, antigen matching, reactive antibodies, medical urgency, and distance. Point allocation for extrarenal organs is based on local listing, donor size, blood type, time waiting, medical urgency, and distance.

The Procurement Process. The crucial element in the donation process is the call from the hospital staff to an organ procurement organization notifying them of a potential donor.

Nearly three quarters of the organ procurement organizations (OPOs) are independent incorporated, nonprofit organizations. The remaining quarter are hospital-based agencies (HOPAs) staffed by transplant donor coordinators, administrators, and specialists. They must be members of the Organ Procurement Transplant Network (OPTN) and must abide by its guidelines and procedures for brain death determination:

- Potential donor is identified by nurses, physicians at participating hospital
- OPO is contacted
- OPO transplant coordinator comes to the hospital to evaluate donor, assist in donor maintenance, coordinate organ procurement

- Brain death diagnosed by authorized physician (OPO personnel may not participate)
- Consent for donation obtained; OPO personnel may assist in completing consent forms and counseling families
- Organs recovered with assistance of OPO surgical team
- Organ maintenance and transport supervised by OPO
- OPO reimburses the hospital on receipt of itemized bill and is reimbursed in turn by Medicare or other payers

The clinical criteria for brain death are as follows:

- No response to external stimuli
- No reflex activity except of spinal cord origin
- No pupillary response to light
- No corneal reflex
- No eye movement with caloric testing or doll's-eyes maneuver
- No gag reflex
- No cough reflex
- Apnea in the presence of adequate CO_2 stimulus

The following seven conditions are some of the criteria used for identifying potential donors of organs:

- Acute neurological or neurosurgical trauma
- Intracranial hemorrhage
- Gunshot wound to the head
- Primary brain tumor
- Drug overdose
- Metabolic disorder
- Cerebral anoxia

Organ donor cards and advance directives can be utilized to indicate the wishes of the potential donor. However, it is generally accepted that if family members cannot come to agreement about donating, even in the presence of a signed donor card, the organs and tissue of that donor will not be taken. That is why it is so important for people who choose to sign a donor card to discuss their wishes with family so that these wishes could be respected at the time of death. In the absence of an executed Proxy Form, family members may give consent to the donation of the deceased's organs or tissue in the following order of priority: (1) spouse, (2) adult son or daughter, (3) parent, (4) adult sibling, (5) legal guardian, (6) other authorized individual.

Influences on the Organ Procurement Process. Standards for donor selection have broadened and become increasingly uniform. Not all that long ago, transplant teams would not even consider a donor older than 55 years of age. With time and medical advances, we realize that physiological age and not chronological age should be the determining factor.

Brain death has become widely accepted as a criterion for the determination of death and it has become customary to employ the brain death standard for the declaration of death.

Organ exchanges across the country have become commonplace as preservation techniques have improved. With the increased ability to preserve certain organs, it is now routine to retrieve organs in one state and transport them to another area where the patient most needs that organ or tissue or is the best match for it. This is facilitated by UNOS and assures that a minimum number of organs are wasted for lack of a recipient.

Techniques for organ removal have changed from predominantly kidney and tissue only to routine multiple organ retrieval. Emphasis has been placed on the aggressive support of the potential donor so that all of the organs may be in optimal functional states. As skill has advanced and more organs can be successfully transplanted, each donor must be supported to the fullest to maximize the number of organs and amount of tissue that can be retrieved from any single donor.

Evolving Issues in Organ Donation

Presumed Consent. In much of Europe the rate of kidney procurement is substantially higher per million than in the U.S. The U.S. average is about 26 kidneys/million of population, whereas Austria (which has presumed consent) reports 57.6 kidneys/million of population. In spite of various legislative initiatives and increased public awareness, the consent process still remains an emotional issue. It is questionable whether we will ever be able to have a presumed consent process in the U.S., even though most major religions do not object to donation and view it as an act of altruism.

Public Image and Myths. The media can be friendly to transplantation, and many human interest stories have been written about its benefits. Yet there have been instances of television productions giving the opposite message. An episode of "Law and Order" showed a man being mugged in the park by a doctor and nurse, who then remove his kidney in an apartment and return him to the park to die. This happens just because a wealthy man wants this kidney for his sick daughter. One "Knots Landing" episode suggests that as long as you have enough money you can buy your way to the top of the waiting list.

Many people fear that donation will result in mutilation of the deceased, that an open casket will not be feasible after organ harvesting, that patients will not be cared for if hospital staff know the patient has signed an organ donor card. All of these beliefs are false, but such fears can only be allayed if the correct information about this issue is readily available and disseminated to the public.

Financial Issues. Financial considerations also have an impact on transplantation. Some involve the sale of organs. In India, where organs are, in fact, for sale, the legislature is now considering making this practice illegal. The issue in the U.S. is whether we should provide financial remuneration for donation. Who would pay; what is a fair price? There are many questions and issues that this provision would precipitate. Should we pay for burial costs? Do you get a tax deduction for donation? Would such payments pressure people who are economically indigent to obtain some ready cash by selling organs?

Sadly, my office recently received two calls from people offering to sell their organs for cash since they were out of work and had heard that you could get good money for organs. They were quite disappointed when we informed them that organ sales were illegal in the United States.

Access to Service. Transplantation is not a service available only to the rich. In most states Medicaid covers transplantation of kidneys, hearts, liver, and bone marrow. Medicare covers all of these, though with some restrictions.

The perception of inequality in access to transplantation is a barrier to donation. Several recent reports, including a report published by the Office of the Inspector General, raise the point of disparity among certain populations. It appears, from the data reviewed, that blacks wait almost twice as long for an organ as whites. There is substantial discussion about what these data really mean, and many questions have been raised about the data. How much is based on racism as opposed to medical issues? What are the economic and social issues with regard to access?

Would this problem be alleviated if minority donation increased? We know that the Bone Marrow Registry has predominantly white registrants. A person who is Asian or African-American has a slim to nonexistent likelihood of finding a match via the registry. This was one of the reasons the government has granted additional monies to the Registry to actively promote minority recruitment. In fact that has been quite successful. The registry had until recently only about 100,000 to 150,000 registrants. They have just reported reaching the 500,000 mark. However, only about 30% of those are minorities. In order to change this situation we need to promote greater ethnic diversity in the donor pool so that all members of society can benefit from transplantation. There are several groups within the United Network of Organ Sharing (UNOS) structure, as well as groups not affiliated with UNOS, that are reviewing this information and developing programs directed at minority populations to remedy the situation. Looking at the cultural differences in the African-American community and the Hispanic community could enhance the consent rate.

Organs are in short supply. Who should receive them? Who should be given priority? Who makes those life-and-death decisions? Although dialysis is available for renal failure, and insulin for diabetes, no substitutes are available for the failed liver, heart, or diseased bone marrow. None of these questions would be pressing if there was no organ shortage.

These concerns must involve the joint effort of healthcare professionals, legislators, patients, and the public to make the choices that are required. Until this occurs we will continue to be faced with many of the situations described by other participants in this symposium.

My final comment, and the one I hope every reader remembers most, is, “Don’t take your organs to Heaven—Heaven knows we need them here!” To refer a donor in the NY area, call 1-800-GIFT-4-NY.

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Infants and Others Who Cannot Consent to Donation

THOMAS TOMLINSON, PH.D.

MOST DONORS, of course, cannot consent at the time of donation, because they are dead. Few solid-organ donors have given explicit prior consent to donation themselves. Typically, consent is given for them by their surviving family members.

But these are not the most problematic cases of donation without consent, for two reasons. First, most of these donors were competent adults prior to the injury or illness that led to their death, and so other people close to them had some basis for judging what their wishes would have been about organ donation. Second, since these donors are dead, there is no longer any risk of harming them, and so there is less at stake morally in guessing wrongly about their real preferences concerning organ donation.

The more difficult cases, therefore, are those where these two conditions are not met: where there is no prior history of individual values on which to make a decision about organ donation; and where the donor is still alive, so that the donation imposes on them some risk of harm. There are various sorts of persons who meet these conditions. Retarded donors are one class, and there have been some commentaries and court decisions on such cases, notably on live kidney donation (1) and bone-marrow donation (2). But I want to focus on another class of never-competent living donor—infants.

The case I will use as a springboard involved Abe and Mary Ayala, whose 17-year-old daughter Anissa was diagnosed with myelogenous leukemia. Without a bone-marrow transplant, odds were 80%–90% that she would be dead within five years. With a matched bone-marrow transplant, her chance for cure would be close to 70%. But the odds of finding a matched unrelated donor are a dismal 1:20,000, and the match they lucked upon refused to donate. Her parents then set about to have another child, first requiring a reversal of Abe's vasectomy, hoping to win the 1:4 odds that the child would be a match for Anissa. In fact, their new daughter, Marissa, was a match, and at about six months of age, in June 1991, had bone marrow removed for implantation in her sister (3–5). According to recent reports (personal communication, Elizabeth Quam, Bone Marrow Program) the transplant was a success and both Anissa and Marissa are doing fine.

Can Infants Already Born Be Used As Donors?

Various arguments might be made against what the Ayalas did. Some of these arguments would be directed against the idea of deliberately conceiving a child to use for organ donation. I will consider these below. Other sorts of objections would be directed against using any infant for bone-marrow donation, whether or not the child was conceived for this reason. I want to consider these sorts of objections first, both because they would apply to a much larger class of cases of never-competent donors, and because the morality of conceiving children for use as donors will to some degree turn on the morality of using infant donors at all.

The Question of Excessive Risk. The first concern to consider is whether using infants as donors subjects them to excessive risk. For some sorts of donation, risks may be appreciable. But the risks of bone-marrow donation are exceed-

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Adapted from the author's presentation at the conference "Transplantation: Ethics and Organ Procurement" at the Mount Sinai Medical Center on March 13, 1992. From the Department of Medical Ethics, Michigan State University. Address reprint requests to the author, Professor of Medical Ethics, at 1550 Ann Street, East Lansing, MI 48823.

ingly small, and well within the range of everyday risks that parents are permitted to expose their children to.

According to the National Bone Marrow Donor Registry, out of over 5,000 donations performed to date around the world, no bone-marrow donor has suffered any long-term adverse effects from donation. The risks are primarily those from general anesthesia, which in adults average 1 death in 15,000 across all patients and facilities. The risk of death from anesthesia of a healthy adult in a top-flight facility would be something closer to 1:40,000. This risk would likely be lower in healthy infants, who are hardier and more resilient to anoxic insults to the brain (personal communication, James Waun, M.D., Board-certified anesthesiologist).

One in 40,000 is about the additional risk of death that would be created by taking the child on a cross-country automobile trip to see Grandma, or driving about town a comparable distance during the year, as calculated from estimated risk of automobile travel reported in *Acceptable Risk* (6). This is a risk that few of us would consider excessive, even on the assumption that few of these miles were traveled for the sake of some vital interest of the child, but rather for the convenience or interests of other family members.

The Question of True Consent and the Canon of Loyalty. A more serious objection would contend that organ donation can only be based on consent, which infants cannot give. The argument here would be parallel to the reasons Paul Ramsey gives against any use of children as subjects in nontherapeutic medical experimentation:

> Morally, no parent should consent . . . [to] nontherapeutic . . . experimentation, [which] must be based on true consent if it is to proceed as a human enterprise. . . . No one else on earth should decide to subject these people to investigations having no relation to their own treatment. That is a canon of loyalty to them (7).

Commenting on the Ayala case, George Annas put it more pithily: “Children are not medicine for other people” (8).

The claim here is that organ donation, like participation as a subject in human experimentation, involves imposing a harm or risk of harm on one person (the donor or the subject) for the sake of another person. If research subjects agree to make this sacrifice, it is morally commendable, but it is not a moral duty, even when the benefits to be gained by others are substantial. The same is true of organ donation, because it too is a sacrifice. To remove organs from infants or others is in a morally suspect way to “sacrifice” them, in the name of a utilitarian calculation which betrays the loyalty we owe to their sacred, individual personhood.

But just what is this “canon of loyalty” that Ramsey speaks of? Certainly, we think that parents have an obligation of “loyalty” to their children, but what is the content of that obligation? We can agree that at a minimum, it means not to sacrifice one’s child for the sake of someone else. That is easy to accept, simply because the idea of “sacrifice” is associated with killing, maiming, or otherwise seriously harming the child. But as already explained, the risks imposed by bone-marrow donation are not of this magnitude, and so do not demand “sacrifice” in any sense that is patently morally objectionable.

An alternative interpretation would be that the demand of “loyalty” requires the duty not to impose any risk on one’s child not of its choosing. But this alternative is clearly unacceptable, because on this interpretation parental consent to most medical treatment would be a violation of loyalty, and presumably it is not, as Ramsey himself allowed. On his view, the only time we are justified in imposing risks on unconsenting incompetents is when doing so is, on balance, to their benefit. Indeed, the several court rulings which have approved live organ or tissue donation from a retarded person for an ill sibling have done so by arguing that it was in the retarded person’s best interest to donate and thereby insure the continuing benefits of the sibling’s companionship, guardianship, and so on (1).

But why, or more accurately, when is consent to treatment not a violation of loyalty? This is a fair question, because there could be consents for treatment of incompetent persons that were nonetheless disloyal—namely, when the choice made for treatment was inconsistent with what we reasonably believed the incompetent person would have wanted. This would be an act disloyal to the values that the person held dear, and which formed part of their self-identity as persons.

By extension, I would argue, consent for treatment of a never-competent child is loyal to them only when it is based on reasonable presumptions about what the child’s values and goals would be relative to the risks of harm and promises of benefit of the treatment. It is only on the basis of such presumptions that we can make claims about what is in the child’s “best interest.” But if this is what permits us loyally to impose the risks of treatment, the same approach should also permit us to impose the risks of organ donation, when it would be reasonable to presume a commitment of the child to the life its donation would save, at very small risk to itself.

It would be a paradoxical "canon of loyalty" owed to persons if we were permitted to act only on presumptions about the incompetent's self-interested values, and not at all on presumptions about the sort of moral values that make persons beings who are specially owed a duty of loyalty. It is not a violation of loyalty, but an expression of it, when I conscientiously strive to make the decisions my incompetent child would make as a mature person, equipped with minimally decent moral commitments to others (9).

One implication of this reasoning is that parental consent for organ donation to a sibling would be more defensible than consent for donation to a stranger, because in the latter case there would be less of a reasonable presumption that the child would feel any commitment to saving that person, as opposed to another family member.

However, a third reason offered against parental consent for organ donation is that when the recipient is another family member, parents are in a conflict of interest as protectors of their infant's welfare. Their love and desperate hope for their other child might blind them to the real magnitude of the harms their donor child would suffer.

This is probably a good argument against relying on parental consent as the sole and sufficient warrant for proceeding with a transplantation. But the real danger it warns against can be blunted by requiring an independent assessment of whether the risks of transplantation are excessively high, so high that we can no longer confidently presume that the child donor herself would want to take the risk for the sake of her sibling. At a minimum, those who are coordinating the donation and transplant should recognize their responsibility to apply standards of reasonable risk to the parents' decision to use a child as a donor. I shall not attempt to work out the details of how a completely adequate independent assessment would be made, except to say that it cannot consist simply in the concurrence of the transplant team, who have their own predisposing agenda (I thank a member of the conference audience for reminding me of the transplant team's conflict of interest.)

Can Children Be Conceived For Use as Infant Donors?

Once it has been shown that using infants already born as live organ donors is not in itself morally objectionable, the main argument to be made against conceiving children for that purpose evaporates. Nevertheless, several other sorts of objections have been made.

The Question of Children as Means. One objection has it that conceiving children as donors uses them as a means, but children should be brought into this world only for their own sake, as ends in themselves: "The ideal reason for having a child is associated with that child's own welfare, to bring a child into being and to nurture it" (10).

Although Marissa Ayala was "used as a means" to save her sister's life, this fact is not by itself morally decisive, both because such use posed little threat to Marissa's interests, and because we had, on the face of it, no cause to doubt that her parents valued her for other reasons as well. She was used as a means (as we all are), but not merely as a means, which is the crucial modifier in the Kantian injunction to respect persons as ends in themselves.

Except for the saintly (who thankfully have few offspring in any event), most of us conceive children out of a complex mixture of motives, when the conception is "motivated" at all. Most of these motives are self-interested, and few of them are as altruistic as the Ayala's concern with saving Anissa's life—all with no palpably evil results. It is therefore naively pious to claim that children "should be conceived for their own worth." Children, once conceived, should then be treated with due regard for their intrinsic worth. But there are no reasons for thinking that Marissa, or any other infant under similar circumstances, would not be so treated by her parents. Except in the most extreme cases, where there is only a single overarching or malevolent motive, there is no natural connection between motives for conceiving children, and later motives and feelings which support nurturance and love—a good thing, too, since the survival of the species has probably depended on it.

The Question of Abortion Used Solely for Donation. Another objection which has been raised is that conceiving children as donors implies acceptance of abortion for purposes of fetal organ donation. After all, if someone with the Ayalas' motives discovered that the fetus they had conceived was not a suitable match, they could just as well decide to abort that one, hoping for better luck with the next. Assuming that we should condemn conception and abortion for the purpose of transplanting fetal tissue, should we not also condemn what the Ayalas did?

This is an obvious non sequitur. Even if we should condemn all such abortions (an arguable assumption itself), it would be because using the fetus's organs requires killing the fetus, and by killing the fetus, we would violate the respect owed to the intrinsic value of fetal life. Using the fetus as a means for organ donation by way of abortion is incompatible with respecting it as an end in itself. Using Marissa as a means for obtaining bone marrow is not incompatible with respecting her as an end in herself. Even the staunch antiabortionist could consistently accept the Ayalas' end, but reject using abortion as the means to achieving it.

Conclusion

Using infants, and by extension, other never-competent persons as live organ donors is not in itself morally objectionable, nor is conceiving children for this purpose. When the risks to the donor are very low, and the never-competent person's loving concern for the threatened recipient is reasonably presumed, the person is not illicitly being used as mere means, nor sacrificed for the good of others.

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Debatable Donors:

When Can We Count Their Consent?

Rosamond Rhodes, Ph.D.

Abstract

Donor consent is the standard requirement for the acceptance of an organ or tissue donation from a living donor. Usually consent to donation is respected as the choice and act of an autonomous agent. There are times, however, when the consent should be paternalistically set aside. The problem for those who must make these decisions is determining when the donor's autonomy should be respected and when paternalistic interference is appropriate. This paper draws on the writings of Kant to develop an autonomy-preserving criterion for determining where to draw the line. It then goes on to display how that criterion could be applied to the case of an adolescent donor who agrees to donate a kidney to his brother.

Whenever a person becomes a living donor, she or he is subjected to some risk, pain, and mutilation. Nevertheless, considering the good it does for another, we usually accept the organs and respect the donor's choice. There are times, however, when a willing donor is refused. When can we count a donor's consent? When do we paternalistically refuse to act on a donor's choice? Why? To set the stage for understanding my answer to these questions, I begin by presenting some hypothetical situations and common intuitions.

If I wanted to cut off my healthy hand, or even just a healthy finger, I imagine that most people would feel justified in interfering and stopping me. I also imagine that I would not be able to find a surgeon who would be willing to perform the amputation for me, even if I were willing to sign all of the necessary consent forms.

If I wanted to donate one of my healthy kidneys to my child who had kidney failure and needed one, people would support my choice and the kidney transplant team would be eager to cooperate. Nevertheless, pressure from other family members and society at large (which raises eyebrows whenever parents survive a fire unscathed while their offspring perish) could be so coercive as to make a parent feel unable to withhold consent. If, however, I wanted to donate my heart to save my child, I am sure the heart transplant team would refuse to cooperate. And if I wanted to donate a kidney to each of my two children who were in need, I imagine that the kidney transplant team would not accept my consent as valid and refuse to act on it.

If I was willing to be a bone-marrow donor for a total stranger, my consent would be accepted and I would be seen as a hero. On the other hand, if I volunteered my 3-year-old child who, when asked, said "yes," or presented my 7-year-old who clearly articulated her willingness to donate marrow to save the dying stranger, it is not obvious whether people would accept their agreement as consent. If these children were agreeing to donate a kidney instead, it would be even more likely

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that people would refuse to count their consent. Yet we might be inclined to accept the consent of one child (or childlike individual) to donate a kidney to the other, and we might even determine that the child's consent was not necessary for the moral acceptability of that donation; recent legal cases have reached just such conclusions (1–3).

I suspect that this survey of responses produces a clear and uniform set of intuitions. When death is a certainty for the heart donor, people reject my consent. When death is only a remote possibility, my consent to a nonmedically-indicated amputation is refused, whereas my consent to kidney or marrow donation, which may involve no less a risk, or even a greater risk, is accepted. So risk itself could not be the crucial consideration.

When it comes to my children, their consent is questionable, making our acceptance of their donations uncertain. When one is needed as the donor for the other, however, the quality of the consent and even the need for consent seem irrelevant. So consent, in itself, could not be the sole criterion for our decisions.

In the latter case of one child donating for the other, the children's familial relation is significant. But personal relationship is unnecessary for the acceptability of my own marrow donation for the dying stranger. Risk, consent, and relationship all seem to be considerations in deciding when to accept an organ donation, but how they fit together and why is not clear.

We do need organ donations to save or improve lives. Does this need allow us to accept the consent of questionable donors (such as retarded or demented relatives)? And why? Although some of our intuitions about the hypothetical cases are clear, the principle underlying the acceptability of some consent is certainly not obvious. Why does agreement sometimes have to be respected? When can consent be set aside? If we accept the prospective donor's consent, we respect their autonomy. If we refuse to accept their consent out of concern for their good, we are treating them paternalistically. Is such paternalism ever morally acceptable?

It is common to see paternalistic action in conflict with respect for autonomy, but there is a way of reconciling the two, as the good parent does. Emmanuel Kant, the nineteenth-century philosopher who focused our attention on the primacy of autonomy, wrestled with this problem of justifiable paternalism. In what follows I adopt the Kantian approach to the issue as it presents itself in modern medical practice. First I lay out a groundwork for understanding the dilemma by presenting a brief sketch of autonomy and beneficence. These mere glosses of the concepts should be sufficient for this discussion, and they are meant to be neutral as to questions of their source or generation. I then present a principle for assessing when paternalistic intervention is appropriate. I conclude by illustrating how that adjudicating principle can be applied in resolving a complex case.

A Brief Sketch of Autonomy and Beneficence

Autonomy. Respect for autonomy is the most fundamental of all (Kantian) principles. It derives from the recognition that what distinguishes moral beings from other creatures and what entitles persons to special treatment are (a) the ability to conceive of moral principles or rules, (b) the ability to choose their actions in terms of conforming with moral rules, and (c) the ability to limit their action to conform with those principles. Having these abilities, which amount to the ability to be moral, is being autonomous. Autonomy, therefore, deserves ultimate respect because it is taken as the ground for both moral treatment and moral responsibility. Autonomous agents each have their own conception of their own good and guide their actions accordingly. Respect for autonomy therefore requires that we allow people to make their own choices.

Beneficence. Beneficence is also a basic principle of (Kantian) ethics, derived from the understanding that anyone needing help would want others to provide it. Since morality demands that we treat others as we would wish to be treated ourselves, we are obliged to treat others with beneficence.

A Principle for Assessing Paternalistic Intervention

Paternalism. With these preliminary understandings of the principles of autonomy and beneficence, we can proceed to an examination of paternalism. According to my understanding of Kant, the problem of paternalism arises because relationships among rational beings in the moral world are governed by both the principle of mutual love and the principle of respect.

The principle of mutual love gives us the "maxim of benevolence," which, for Kant, entails the "duty to love one's neighbor" or "to make the ends of others (as long as they are not immoral) my own" (4). The second principle, respect, charges us to limit our self-interested behavior in order to preserve the "dignity of humanity in another." It entails the strict "duty of free respect to others," which is analogous to the duty "not to encroach upon their rights." Whereas mutual love constantly directs people "to approach one another," respect directs them "to keep themselves at a distance." The duty of benevolence seems to require involvement in the lives of others; respect seems to require that we leave others alone. The problem for the autonomous agent—as for example the health care provider—who governs action according to these principles of duty is to determine when paternalistic action, as in action that interferes with a patient's choice, satisfies the requirements of both mutual love and respect.

Assessing Autonomy in Others. When considering paternalistic interference, a reason for presuming that the other is capable of making an autonomous choice is sufficient for attributing autonomy. A sufficient reason for requiring that another be respected as an autonomous agent would be their demonstration of self-motivated action, or voluntary behavior. Stated negatively, and more to the point, only reasons for concluding that the other is incapable of making an autonomous choice (the particular one in question) could justify a particular paternalistic interference.

This standard presents a strong presumption in favor of regarding others as autonomous beings, capable of making rational choices relative to their own goals. Even when another's choice strikes us as a bad idea, foolhardy, or dangerous, for the most part we must respect it and leave others alone to take whatever risks they choose. In Kant's framework, we are bound to "cast a veil of philanthropy over the faults of others" (ref. 4, 466). Respect for the other as an end in himself requires us to presume, whenever possible, that his action is autonomous. We have "a duty to respect man even in the logical use of his reason: not to censure someone's errors under the name of absurdity, inept judgment, and the like, but rather to suppose that in such an inept judgment there must be something true, and to seek it out" (ref. 4, 463).

In other words, as far as possible, Kant demands that we try to consider others' actions as if they were freely done from an autonomous will. Respect requires us to try to think of what another does as something we too would find reasonable if only we knew the facts of the situation as we should imagine the other does.

Obviously, since paternalistic interference is ideally applied before another's autonomy-threatening act could be performed, in some cases the other's choice could be the salient consideration. We could decide that although there was no independent reason (such as known intoxication or psychosis) to suppose that the person lacked the capacity for autonomy, if this particular choice were enacted the person's future autonomy would undoubtedly be compromised and, furthermore, we might be unable, despite a sincere effort, to conceive of a rational end that the imminent chosen action might serve. In some cases (as Kant might argue) an assessment of the other's capacity for autonomous willing is the paramount consideration: a person might be either incapable of willing at all or incapable of reason.

In each situation, after finding the other's choice inappropriate or capacity inadequate, the paternalistic agent must ascertain whether or not failing to interfere would make the other's future autonomous action impossible. If so, the agent would be morally bound to perform the paternalistic act of beneficence. On the other hand, when there would be no irremediable effect on the other's autonomy, regardless of how foolish or undesirable one might think the action, "[w]hat they count as belonging to their happiness is left up to them to decide" (ref. 4, 388).

The end of the other's continued existence as an autonomous being, therefore, serves as the limiting conception for paternalism:

- When autonomy can only be preserved by paternalistic action (for instance, stopping me when I want to cut off my own hand), because it preserves autonomy, the only thing which has absolute worth, we must interfere.
- When a person's capacity for autonomous action is intact and can be expected to remain so (as when I want to donate marrow to a stranger) paternalistic interference would not be justified, since autonomy is not jeopardized.
- If, however, there is no possibility of preserving autonomy (for example, if the requisite mental status can never be restored, since the brain has "liquified"), no duties *qua* "end in itself" can be owed to the other.

Tests for Appropriate Paternalism. Physical welfare as well as psychological well-being (ref. 4, 393–394) count as needs which must be met for continuing agency. Seriously compromising either (but not merely making oneself somewhat worse off or somewhat diminishing one's chance for continued agency) would make future autonomous action impossible. These autonomy-preserving justifications for paternalistic interference explain why Kant sees "minors and the mentally deranged" (ref. 4, 454) as broad classes of people who are generally exempted from the autonomy-respecting rule. Without autonomy-preserving paternalistic interference, the future autonomy of minors can be jeopardized. Without such interference, the temporarily deranged might never have their autonomy restored.

Besides referring to needs as a test in determining the appropriate domain for paternalistic interference with another, we can also rely on a model of hypothetical assent. In judging whether an act of paternalism would be my duty, I would invoke hypothetical assent and ask whether, as a rational being, one could possibly assent to the other's proposed action. Paternalistic interference would be justified if the paternalistic agent were to find that he could not "contain the end of this action in himself."

To illustrate the employment of this model, again consider some examples. Paternalism would be justified when I wanted to cut off my healthy hand. Because an agent could not imagine any end which she or he might adopt that would motivate such an action—that is, hypothetically, could not conceive of himself or herself assenting—the agent must paternalistically act to preserve autonomy and stop me from severing my hand. Paternalism would not be justified for the bone-marrow donor because an agent could imagine a rational person assenting to accept some pain, scarring, and inconvenience to save another's life.

This hypothetical assent test differs from other models for delimiting paternalism which rely on hypothetical assent (5–7) in that it does not ask the paternalistic agent to conceive what she or he could not know—whether the beneficiary would or would not assent, which is the test invoked in "substituted judgment." Hypothetical assent is assessed straightforwardly, on this view, according to one's own conception of what would gain the assent of any rational agent. (Concern about the patient's idiosyncratic views, personal history, previous statements, and so on, have limited relevance according to the rational agent perspective, whereas they would count a great deal for those who base hypothetical assent on a determination of what the particular beneficiary would have wanted. Furthermore, healthcare workers must always be alert to the possibility that their own personal history may influence their view of rationality. It is the view of rationality, rather than the view of the patient's or healthcare provider's idiosyncrasies, which may justify and direct paternalistic interference.)

The need test and the hypothetical assent test for the appropriateness of paternalism relate in a typical Kantian fashion to the form of the agent's willing rather than to external criteria of the "beneficiary's" condition. Instead of requiring proof of the other's lack of rationality or competence, the moral standard demands only a sincere effort to test one's judgment by the autonomy-preserving principle of paternalism.

Application

With the autonomy-preserving criterion for paternalistic interference in mind, let us examine the complicated case of a 17-year-old who is the best organ match for his young brother with kidney failure. Although a transplant from this sibling would appear to be the optimal medical choice, the moral acceptability of that option is certainly not obvious. The consequences of taking and not taking the kidney need to be considered, and we also need to review the moral principles bearing on the case. (A similar case was debated for several weeks in 1991 at the weekly Mount Sinai Kidney Transplant meetings chaired by Dr. Lewis Burrows; see ref. 8.)

Case Report. The potential donor, David, wants to donate a kidney to his brother, Ken. He understands that the procedure presents some risk for him and that after surgery he may no longer be able to continue playing football. His idols have all been football players and he now plays on his high school team. Nevertheless, he agrees to be a donor as soon as the option is mentioned, and he never displays any ambivalence. He says, "I want to donate my kidney because then I'll be a hero to my family." This close family, of two parents and five older siblings, strongly supports the 17-year-old's decision, especially after an older brother is found medically (anatomically) unsuitable.

The parents and two of the older siblings could also be medically acceptable donors. However, their organs are likely to be better grafts (one haplotype matches) than a nonrelated cadaveric kidney, but they are less compatible than the perfect organ match (haploidentical) that could be provided by David, the adolescent brother. Studies have shown that in the short run there is little difference in the survivability of organs from different classes of donors. After several years, however, there is a significant difference, perfectly matched kidneys being much less likely to be rejected than less ideally matched organs (9).

Case Discussion. Using the autonomy-preserving principle of paternalism, should David's choice be respected or should his donation be refused? The answer is determined by the assessment of whether David's organ "donation" reflects an autonomous choice. As an autonomous choice it must be respected, and we must accept his donation. Viewing his decision as a nonautonomous act, we would have to consider how transplanting his kidney might affect his future autonomy.

Although morality usually requires us to presume that the decisions others make are autonomous, the choices of children are the classic exception to that rule. We always feel duty bound to evaluate our children's acts, to teach them how to think—a particularly Kantian example, as in his "The Didactics of Ethics," (ref. 4)—and to protect them from the predictable harms of their choices (for example, maiming). We do this so that when our children become autonomous, they will be free of handicaps and able to do what they choose. Adolescents fall into a gray zone where it is unclear whether to assume that they need paternalistic protection or that they are fully autonomous. Often the justifiable presumption is that the adolescent's autonomy status is somewhere between childhood and maturity. In these cases, choices with the most serious consequences should be examined; some of their choices should be respected and others constrained. The autonomy-preserving principle of paternalism informs us that the likelihood, extent, and degree to which predictable harms might restrict future autonomy determine whether an adolescent's choice should be restricted or respected.

We are left with the same two questions: (a) Are we entitled to assume that David's choice is autonomous? (b) If David's choice is not autonomous, will donating his kidney limit his future autonomy? David's age and the apparent unwaveringness of his resolve to donate might lead us to judge that David is acting autonomously. There are, however, several reasons for concluding that David's decision might not be autonomous. David's stated reason for being a donor—that he would be a hero to his family—seems immature. Also, adolescents are notoriously emotional and easily swept away by emotional causes. Bernstein and Simmons mention several striking, atypical features of the adolescent donor's decision-making process. According to them, rapid decision-making and a lack of ambivalence seem to characterize adolescents' decisions to donate a kidney. In fact, 50% of the potential adolescent donors hearing about the need immediately volunteered to be donors. Furthermore, Bernstein and Simmons claim that " 'black sheep' are particularly likely to be motivated to donate in order to regain status in the family" (10). The tremendous emotional component of this situation might have an overwhelming impact on David's choice. Furthermore, David's close family, which strongly supports his donation, might have had a powerful coercive effect on his decision.

Being an organ donor would certainly restrict David's future choices. Continuing to play football would no longer be an option for him. Other career opportunities, in particular those which might be most attractive to a young man who enjoys contact sports (military service, law enforcement), might be blocked because they typically have strict physical standards for acceptance. The possible psychological impact of the kidney donation might also limit what David may do in the future.

Determining that we should not assume David's choice to be autonomous and that his "decision" to donate would be likely to limit his future autonomy requires paternalistic interference to protect David. It would prohibit transplanting his kidney now. On the other hand, determining that we should assume that David is autonomous would, instead, leave us with the duty of respecting his choice and require us to transplant his organ to his brother.

Conclusion

Whatever the particular conclusion in this case turns out to be, it cannot be generalized to cover other cases involving adolescents, children, infants, or fetuses. In other cases, the facts might determine a different adjudication of the conflicting principles, and in some situations, additional principles might be pertinent. Nevertheless, in all cases where autonomy is absent and someone will suffer harm for the benefit of another, the least we owe them is a serious evaluation of the ethics of inflicting that harm and a willingness to refuse cooperation when we recognize that cooperating would be immoral.

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The Physician's Experience:

Cases and Doubts

Steven M. Fruchtman, M.D., Harry Schanzer, M.D., and Myron E. Schwartz, M.D.

Cases in Bone Marrow Transplantation

Steven Fruchtman, M.D.

Two cases in bone-marrow transplantation are, I think, a natural continuation of the discussion of donors and consent by Angelina Korsun, Thomas Tomlinson, and Rosamond Rhodes.

Case 1: True Consent and Reliability. A 44-year-old gentleman came to his physician with a white count of 350,000 cells/nL. A diagnosis of chronic myelocytic leukemia was made on the basis of bone marrow histology and cytogenetics. He was managed medically for two years and then referred for marrow transplantation. He had two siblings, but only one was HLA identical and thus appropriate for marrow donation, his 46-year-old sister who was institutionalized with chronic schizophrenia and was taking a multitude of psychotropic medications.

Thus, one of the issues was informed consent. Could we actually explain to the schizophrenic sister what she was going up against in marrow donation, and was she competent to understand the procedure?

The other issue was reliability. After HLA typing, further medical evaluation of this woman was required. In addition, she frequently did not appear for her medical appointments. Sometimes she said she just wasn't feeling up to it. At other times, she felt that things were not appropriate at her institution and she demanded some changes be made before she continued to cooperate with the procedure. Remember that once the recipient is prepared for marrow transplantation, he or she will no doubt die from complications of the preparative regimen if the marrow donor does not show up at the appropriate time, and if the marrow donation is not given on the scheduled day.

A third issue, related to reliability, was whether or not a backup marrow should be obtained from the leukemia patient in case the marrow donor did not show up on the designated day. If she did not show up, the only way to rescue him after he had received total body irradiation in preparation for the marrow transplant was to reinfuse his own bone marrow, with its leukemia. The only thing we would have accomplished, if that happened, would be to return his leukemia to him.

So we had problems with informed consent and with the reliability of the only marrow donor available for this man who had leukemia.

Case 2: A Debatable Young Donor. A 4-year-old patient with acute lymphocytic leukemia had undergone induction chemotherapy and was put into remission for his leukemia. In the next year, his leukemia relapsed four times. Each time he received further chemotherapy he went back into remission and was referred for marrow transplant to another institution.

While on the waiting list for marrow transplant, the patient developed leukemia of the central nervous system, and the marrow transplant had to be delayed. The central nervous system leukemia was eradicated and he was again referred for transplant. His only HLA-identical do-

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nor was his 3-year-old younger brother. The parents gave consent for marrow donation, and the patient underwent marrow transplantation. The transplant was complicated by fungal infection and graft-versus-host disease. Unfortunately, three months later the patient's leukemia returned. The initial marrow transplant center recommended that no further therapy be given, and he came to this institution for a second opinion about another marrow transplant.

We felt that perhaps—and I emphasize "perhaps"—the patient could be helped by another marrow transplant, because up until that point he had only received chemotherapy. Our preparative regimen included a total-body irradiation approach, and his leukemic clone had never been exposed to radiation. A major issue was that the only available marrow donor was his now 4½-year-old younger brother, who had already donated marrow for his sibling. He would have to once again undergo general anesthesia and marrow donation for the remote possibility of helping his sibling with refractory leukemia.

For infants, marrow donation is a little more risky than for adults. We try, because of the young age of these patients, not to transfuse them with blood-bank blood. However, because they are very small, it is difficult for them to donate blood for themselves, and thus when we harvest their marrow, they become profoundly anemic. They can have a hematocrit of 18%–19% post harvesting. This does increase the risk for the procedure.

The ethical question in this case is whether to ask a 4½-year-old child to once again undergo general anesthesia and donate marrow for his sibling with leukemia. The chance of the second marrow transplant curing the patient of his leukemia was small.

Child-Donor Kidneys
Harry Schanzer, M.D.

Case Presentation. A 26-year-old woman, blood group O, who had end-stage renal disease secondary to lupus erythematosus was treated with dialysis beginning in March 1990. She was placed on the cadaveric kidney transplant list in August 1991. On February 1, 1992, a double en bloc set of kidneys from a 10-month-old baby donor who died after suffering child-abuse trauma was offered to our institution for transplantation to this patient. The transplant went uneventfully and the patient initially did well. On the seventh postoperative day she developed acute pain in the area of the transplant, and had an increase in creatinine. A renal scan demonstrated lack of uptake to the medial kidney. On surgical exploration, an infarcted kidney was found and nephrectomy of the affected medial kidney was performed. In follow-up, the patient has done well, and is stable, with a creatinine level of 3.5 mg% one month after transplantation.

Background. At the beginning of 1990, about 20,000 patients with end-stage renal disease were waiting for a kidney transplant. During that year, only about 7,500 cadaveric transplants and 2,000 living related transplants were performed. This shortage of kidneys has become more severe with time. In the United States the rate of kidney transplants (number of transplants for every 1,000 patients on dialysis) has been decreasing since 1988. This national reality is even more severe in New York State.

There is, therefore, a great need for maximal utilization of the potential donor pool.

The results of transplantation of donor kidneys from children younger than 4 years of age have been inconclusive. The small size of the kidney and its vessels and ureter presents problems of adequate renal functioning mass and poses difficult technical challenges. Reports from Minnesota establish that long-term results of child-donor en bloc kidneys are similar to those obtained with adult-donor single kidneys. A recent report from St. Louis showed good one-year and two-year graft survival in five cases. The rate of technical complications nevertheless was quite high: in three patients one kidney was infarcted, in two of them a uninephrectomy had to be performed. In Mount Sinai over the past eight months, we have performed seven of these transplants. In two patients, both kidneys were lost to infarction. In two other patients, one kidney had to be removed due to infarction. The three remaining patients did well, with no complications. At this time, with a follow-up of one to nine months, five of the seven patients are doing well without dialysis.

Ethical Questions. These cases pose a particular ethical question: During the process of informed consent, should the patient be told about the characteristics of kidneys donated by children and the potentially more complicated course and lower success of such transplants?

These cases also bring out a more general question: Should patients be informed about the quality of the organ or organs to be transplanted?

Living-Related Donation of Liver Segments: Is It an Option?
Myron E. Schwartz, M.D.

The case of a 15-month-old boy with end-stage liver disease probably due to congenital biliary atresia is a starting point for this discussion. Due to his condition, he has suffered developmental delay, and through the second half of 1991 he began to develop signs of liver failure. He was referred for transplant evaluation in December, and was placed on the waiting list for a cadaveric donor organ the first week of January.

The patient has been hospitalized since being listed for transplantation, and has been deteriorating steadily. In order to increase his chance to get a liver, we increased the weight range for donors that we would consider, agreeing to split a larger liver if necessary to provide an appropriately sized graft. Despite this, however, we have been unable to come up with a suitable organ, and the patient now hovers near death in the intensive-care unit. The question has been raised: "Should we approach the family about the possibility of donation by one of the parents of a portion of the liver?"

Living-related organ donation has long been practiced in kidney transplantation. A kidney may be removed with a high degree of safety, and with little measurable long-term effect on the donor. Living-kidney donor mortality has been reported in the range of 0.1% or less. Such a range must be the case for us to justify the procedure to ourselves; we must ever be mindful of Hippocrates' admonition, *primum non nocere,* first do no harm.

Safety. Whether a portion of the liver can be removed with such a high degree of safety is a matter of conjecture. No reported series of partial liver resections matches these statistics, but then liver resection has not generally been performed on young, healthy donors with normal livers. It is a relatively small portion of the liver, the left lateral segment, that needs to be removed for this procedure. The techniques for this procedure are well standardized, and are similar to methods that we use routinely in the treatment of patients with liver cancer.

Based on our experience, we feel that the donor operation could certainly be performed with less than 1% mortality. Because of the organ's known remarkable regenerative capacity, within 6 weeks of surgery the liver will have reattained its preoperative size and function, so that no long-term negative effect on the donor is anticipated. This patient's 22-year-old mother and 28-year-old father are aware individuals who are in good health. In the past, they have made inquiries about the possibility of donation to members of our staff.

Recipient Complications. There are potential complications to the recipient inherent in the use of a portion of a liver for transplantation. Using reduced-size grafts, that is, taking an organ from an adult cadaver donor and cutting away a portion of the liver to an appropriate size, has been performed in many centers, including Mount Sinai. Problems with bleeding and infection have arisen because of the cut raw surface of the liver graft, but overall patient survival has been similar to that achieved when whole organs are used.

This drawback is also a factor in living-related transplantation. In the reduced cadaver graft, the main blood vessels of the donor liver can be preserved to make the connections to the recipient vessels; in the living-related procedure, the main vessels to the liver must of course be left in the donor. This makes it necessary to perform additional delicate vascular reconstruction of the graft before implantation, slightly increasing the risk of clotting, a serious complication that may lead to graft failure.

Theoretical Advantages. There are theoretical advantages to living-related donation. An organ from a relative will provide a better match between the graft and the recipient, possibly reducing the chance of rejection. In about 5% of cadaver transplants, the organs do not work, presumably because of unrecognized problems in the donor or because of the need to preserve the liver for extended periods of time. In living-related donation, the donor is known to be alive and healthy, and the graft can be taken out of the donor and placed into the recipient almost directly, minimizing the time that the graft is without blood supply. Finally, the establishment of a living-related program would permit the elective transplantation of candidates who are medically stable, rather than having to wait until the recipient is in extremis. In our experience, the most significant predictor of survival following transplant has been the pretransplant medical status of the recipient.

As of today, living-related liver transplantation has been performed in only one center in the United States. It has been undertaken in a number of other countries where there is no brain-death legislation, thus preventing cadaveric organ donation. At the University of Chicago, over 40 liver transplants have been performed. There have been no donor deaths, although one donor, the first, required splenectomy. Recipient survival is about 90%, a bit better than Chicago's overall results, although favorable cases were selected early in their experience. No increase in complications has been observed in the Chicago series.

Reasons for Reluctance. Other transplant centers have been reluctant to initiate living-related liver transplantation. The primary reason has been concern over the safety of the donor operation.

The argument is also made that, with reduced-size cadaver grafting, there is not a great need for the living-related procedure. Before reduced-size grafting, about 30% of children placed on waiting lists for transplantation died before they received a liver; with reduced grafts, the figure now approximates that for adult candidates, about 10% nationally. In New York, there is a universal donor shortage, and the waiting period for an adult liver now averages about 4–6 months; 15% of our patients listed for transplantation last year died waiting.

Concern has also been raised over the ethical validity of consent for this procedure. As compared to kidney donation, where the alternative is continued life on dialysis, the alternative to liver transplantation is death. Some question whether, in this setting, donor consent can truly be given. The coercive pressure of the situation of greatest need, where the potential recipient is critically ill and death is imminent if transplantation is not performed promptly, would make the voluntary quality of the consent even more questionable.

Is It an Option? We have not yet offered the option of living-related donation to this family. We have gone to Chicago, observed the procedure, and feel that it is well within our technical capability. We feel the pressing need to look for solutions to the critical shortage of donor organs in New York. We welcome the opportunity to lay out this option before the medical community in this forum.

Cases and Doubts

Panel Discussion

Moderator: Daniel A. Moros, M.D.

Daniel A. Moros: We'll start off with the panelists questioning one another a bit and then bring the audience in as well. I'll begin by asking those who presented cases whether they have any specific questions to address to any of the panelists on their cases.

Steven Fruchtman: Given the benefit-risk ratio of marrow donation for a second time in a sibling with end-stage leukemia, how do you go about advising the parents?

Thomas Tomlinson: As you mention in presenting your case, I think one of the significant issues here is the very much lower chance for transplantation success in second and further attempts. If the marrow donation had been perhaps the first time around, then I think I would have a problem with it for the reasons I explained in my talk. Given the much lower prospects of success after the first attempt, I think presuming any kind of consent on behalf of the child who will be the donor is much more difficult because the procedure would be more of a gamble.

I think I would also want to know whether the donor of the second donation faces any extra increment of risk. If so, that would also be an important factor. If risk was simply on a par with the first donation, then I guess I would want to encourage an open and frank discussion with the parents about what the actual prospects were for success the second time around and ask them to balance the risks to the donor.

Fruchtman: My best "guesstimate" would be that the risk of second marrow donation, including the general-anesthesia risk, medically is similar to the first donation. At that time, we had little data to go on because there was little experience with second-marrow transplants for refractured leukemia. In first transplants for refractured leukemia, the chance for long-term survival was 40%–50%. We really didn't know the numbers for second transplants. Our best "guesstimate" was given to the parents as probably less than 10%, probably even as low as 5%, long-term disease-free survival with the second transplant.

I can give you follow-up. The parents decided to permit the 3-year-old to donate marrow for a second time. The marrow was obtained. The donor was listless for a few days, but eventually he was discharged and suffered no long-term sequela of the second marrow donation. The recipient now is six years out from the second marrow transplant with no evidence of leukemia.

Tomlinson: Nice ending.

Moros: All the cases presented have raised a question that is not considered in the theoretical talks: Should organ recipients be informed of the details and risks of transplantation, and should they be invited to accept such risks? Since both Dr. Schanzer and Dr. Schwartz have raised this question, I invite them to offer their opinions.

Harry Schanzer: The problem that I tried specifically to attack is the problem of how much the recipient should know about what he's getting into and how that knowledge logistically influences the work of the transplantation community. At first glance, one would think that the patient has the right to know if he's going to get a kidney of inferior quality, and he has the right to decide if he wants it or if he doesn't want it. The problem is that one has to assess this issue against the

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background of the shortage of organs. Establishing lists of patients who will accept certain kidneys or certain organs raises additional problems. Patients who are very sick are going to take whatever is available. Patients who are very intelligent are going to wait for their best chance. I think that has some ethical implications.

I would like to hear from Dr. Schwartz whether he tells his patients about the condition of the liver to be transplanted into them.

Myron E. Schwartz: On the liver transplant circuit we stand behind our livers. We don't use livers that we don't expect to work. In fact, in analyzing our results and in looking at the results of others, it's been extremely hard to come up with solid predictors of liver function. Because of the overall shortage of organs, certainly we've widened the criteria for acceptability of livers. We've raised the maximum donor age, for example—the oldest liver we've used so far came from a 71-year-old. It worked very well. We've also broadened the variety of circumstances of death and abnormalities in either liver function tests or history of the donor that we will accept. We found that most of the criteria developed in the early days of transplantation about donor acceptability turn out to have no real basis in any facts when it comes to how the livers work.

I don't know how publicly I should say this, but if we have a 65-year-old donor I tend not to channel that organ to a teenage recipient but rather to an older recipient. But the livers work regardless.

If that were not true, however, I would not be telling patients, "You're getting a bad liver" or "You're getting a good liver" because I think of donated livers as a pooled resource. The patient is listed for a transplant and they're going to get a transplant out of this pool. Fifteen percent of patients are never going to get a transplant; they're going to die. To me, it's not one person to one organ; that's not the way I view it. The donated livers are a community resource, and the patient gets on the recipient list. We have to do the best we can to get everybody transplanted and not be telling people they'll be getting a good or a bad liver.

Schanzer: We in kidney transplants also stand by our transplants. I think the problem is that we are always working, as somebody in this group has said, on the cutting edge. When we decide to widen our criteria and begin to take kidneys from a donor who is 70 years old, we don't at the time have the evidence that that kidney will work as well as a younger one. So the question really remains: should the patient be told about the uncertainty of that organ compared with the norm that we have? I think that this is where the ethicists would help us.

Rosamond Rhodes: We had this discussion in a kidney transplant meeting. Somebody from the team—I believe it was Dr. Winston—came up with an answer that I thought was very insightful. He suggested that, in terms of informed consent, when patients are registered as candidates in this program, we should inform them of the parameters of organ acceptability; for example, we will accept en bloc kidneys, we will accept kidneys from aged people or organs that may be hours postharvest. That should be part of the informed consent. But once a person accepts the general criteria, they've given up the right to choose an individual organ offered to them. I thought that suggestion met both the criteria of informed consent and the sense of justice of distribution that Dr. Schwartz mentioned.

Tomlinson: I guess I would endorse that, with the addition that I think the patient should be able to control somewhat what sort of organs would be acceptable to them, especially when there are other alternative forms of treatment available—where going under transplant means leaving some other form of treatment which they might find satisfactory compared to the lower chances of success from one kind of graft over another. So I think patients should have some control over that. I think it should be understood, however, from the outset what those parameters are.

Rhodes: I don't think you can have it both ways. A patient can have control in saying, "Well, these are the parameters at Mount Sinai; perhaps Nebraska has more strict criteria because they have a greater organ pool." But either you sign up here or you don't sign up here. That's where the choice comes in. You can't pick and choose between organs.

Tomlinson: I don't think that that's a choice which most patients in fact have. So that's a nonchoice. Of course, patients are not setting the parameters for the transplant team; they're setting the parameters for what goes into their body. I guess I think patients have a fundamental right to choose parameters for themselves. Now, stricter parameters may lower their chances of actually finding a matched organ. But that should be a risk that they are helped to understand. That's part of the trade-off that they should be willing to accept if they want to set parameters.

Rhodes: If a patient were to refuse the bloc kidneys, would he stay on the top of the list or go to the bottom?

Tomlinson: Well, if they refuse to accept the bloc kidneys, they've already lowered their chances of getting a match.

Rhodes: But do they stay at the top?

Tomlinson: Well, they haven't gotten the organ that they require.

Rhodes: They haven't gotten the organ they require, but would they still be left at the top?

Tomlinson: Some organs that are available do not HLA-match. It doesn't mean that I get knocked down to the bottom of the list if they're refused on my behalf.

Moros: Let's let the audience in a bit. I see Margaret Kadian, the senior clinical coordinator of the Mount Sinai Program for Liver Transplantation, wants to comment. Margaret?

Margaret Kadian: When patients agree to be put on the list, we have made a contract with them that may extend to other variables that we haven't even addressed, for example, participation in surgery by a resident or a junior attendee, and whether the donor had cytomegalovirus. These are big contracts and there are a lot of variables, including the quality of the organs. Do we tell everybody every detail? Where do you draw the line?

Tomlinson: It seems to me that we have taken the last generation or so to get to the point where people are allowed to make their own choices. It used to be that when patients came to the hospital they were presumed to have agreed to take the whole package. In transplantation what has happened to informed consent?

Angelina Korsun: I'd like to clarify one point. As Margaret Kadian explained, the fact is that each and every patient is informed of the risks. Everyone is told, "Yes, you may have an infection; it's likely that you'll have some sort of episode of rejection; the treatment may work; it may not work; you may have graft failure; you may need another transplant." That is, in fact, explained. Patients are forewarned that they may need to be on extensive medication prophylactically because of cytomegalovirus or something else.

I think one of the issues is how far do you go in explaining the details of each and every donor? Because you can also take it one step further and say, "Well, I'm white. I don't want a black kidney. I don't want a black liver." Is that right? Is that good? Or, "I'm going to designate that my organs will only go to a person of my choice, of my ethnic background, of my whatever."

Fruchtman: I think that Dr. Rhodes has eloquently discussed the difference between autonomy and paternalism. I think medical dilemmas should be shared with the patients. I find that patients frequently help me make these very difficult decisions if I give them the information they need. I'm not sure whether getting a "white" kidney or a "black" kidney is a medical issue. I haven't seen a physician who knew the donor's race, so there's no way a patient can. Perhaps HLA, antigens, and other medical compatibilities may be an issue, and I think patients have a right to that information. If a possible infection, different from the typical things that recipients are exposed to, is a medical issue, in that particular case, patients have a right to be informed. I believe they have a right to take part in the decision-making process in such cases.

Tomlinson: I endorse that point, and I want also to add that the patient who might want to limit her risk by limiting the sources of organs or tissues that she finds acceptable is also taking a risk. She's taking the risk that she's going to have less of a chance of finding a suitable organ. That's a trade-off. It's a value-laden trade-off, and it's precisely the kind of trade-off that informed consent is supposed to protect as a right of patients to make rather than physicians to prevent them from making. That strongly supports as a standard that we provide information to patients and we provide them some choices at the outset, with full explanations of what it is they're getting into.

Schanzer: As a transplant surgeon, I try to be practical. My interest is to transplant as many patients who need kidneys as I can and give them the best chance of success. Logistically, if I begin to inform each patient of the risks they're going to incur in getting a particular kidney, I'm going to provoke havoc. I'm going to have to throw a lot of kidneys into the bucket because they're going to get old and nobody's going to take them. Or I'm going to divide the population into patients who will get young, good kidneys and other patients who are not so intelligent who are going to get terrible kidneys—which I think is unfair.

I think the patient has the right to know what he's getting into, but not hours before the transplant, because at that point he's emotionally disturbed and he's not objective in analyzing his chances. The patient has to be told at the time of education, letting him know what he's getting into, what we're doing, why we are doing it, what the risks are, and what's going to happen. I don't think it's ethical at that point to divide the patients into ones who will take good kidneys and ones who will take bad kidneys because I think that that's ethically unacceptable. The patient has the right, if he doesn't want to go on our list because we take en bloc kidneys, to go elsewhere. But I don't think that it's practical, at the end of the road, to subject the patient to the dilemma, "Do I accept this kidney or not?"

Rhodes: I agree with almost everything Dr. Schanzer says, but I want to make a distinction here. Usually we let people have choice about what they want, but we're not in the same kind of situation of scarcity. Because there aren't enough organs to go around, they're being distributed as a social resource, distributed according to what purports to be a just policy for distribution. And in such a situation, we have to accept certain limitations. If you want to be part of the system, you can. If you refuse being part of the system, don't get a kidney in our system. Go someplace else. There might not be any other place. So I think it's appropriate to say such things to these patients, while we wouldn't say such things to a patient who's coming in for an appendectomy.

We can inform them of what the social policy is. And here's where I differ somewhat with Dr. Schanzer. Perhaps even just before the transplant, if a person knows that this particular organ is one of those—whatever "those" is—of a relevant medical kind, the patient can refuse to be part of the system at that point too. Just like anybody could decide at any point that they don't want to take any liver at all. Even if it's the best one, they can decide that they don't want to go through with it. A person can decide that they won't take this kidney. But then there are consequences to be borne: they get treated like somebody else starting fresh on the list. They may not live long enough to get their organ, or they'll have to live for years more on dialysis treatment. So I would like to tell them before they get the transplant, but certainly tell them after they get the transplant, "Well, you've gotten bloc kidneys and you may have these extra problems which we're going to be looking for and paying attention to."

Tomlinson: If you think that they should be told before they have the transplant that this organ may pose a special risk, then great. Then we've got informed consent.

Rhodes: But they're not picking and choosing.

Tomlinson: Yes, they are.

Rhodes: They're not picking and choosing this kidney rather than the next one.

Tomlinson: Well, of course they don't pick and choose; they refuse. That's all they've ever been able to do. That's all I was proposing, that they be able to refuse depending on what their own assessment was of relative risk and benefit of confining or limiting the pool of organs that they're willing to accept.

Those Who Don't Give

DENA S. DAVIS, J.D., PH.D.

IMAGINE that you are the transplant coordinator for your hospital. One of the people on your list is in dire need of, say, a new heart, but his other organs are healthy. In the course of his preadmission studies, as part of a general discussion of advance directives, you ask if he would be willing to donate his healthy organs to others in need, should his heart transplant fail. He refuses. We can imagine that his refusal is based on one of a variety of reasons:

- perhaps he fears that the medical staff will be less committed to fight aggressively for his life if they know that they can harvest his organs for others
- perhaps he belongs to a religious group which believes that only intact bodies will be resurrected
- perhaps he is being solicitous of his family members, who have themselves declined to sign donor cards and who are just gut-level uncomfortable with the idea of strangers walking around with their son's body parts

As transplant coordinator, you are painfully aware of the acute shortage of organs; every week, you see people die who had had a good chance of life if an appropriate cadaver organ had been available. How do you feel about this young man? Perhaps, if only at the subliminal level, you find yourself shading the various subjective elements of patient selection against him. You might wonder aloud if someone who does not trust the medical staff will really comply with his post-transplant regimen, or question if someone whose religion forbids organ donation will do well psychologically as an organ recipient. Or do you wish you could institute a hospital or even network-wide policy requiring that only people willing to give are eligible to receive? What kind of policy would you want to formulate?

If we are uncomfortable with this hypothetical patient, it must be because our gut sense of fairness is outraged. We perceive this patient as a free rider: someone who wants something for nothing, who wants the benefits the system can provide but is not willing to "do his share."

I propose to analyze this notion of the free rider, and to show that it is intensely problematic. I will do this in two stages. First, I will raise some questions about the distinctions between "don't," "won't," and "can't," and then I want to show how our gut intuitions about free riders fail in the context of organ allocation.

Don't, Won't, and Can't

What do we mean by someone who "won't" donate an organ after death? Whom would we place in this category? The easiest person to place is perhaps the hardest to imagine: the organ recipient who says, "I don't want to donate—I have no particular reason—and I am too lazy to think about it." Moving along the continuum, we might be a little less quick to categorize the person who admits that she ought to think about it, but claims that the whole subject "gives me the shivers," so she refuses to pursue it further. If she or a loved one were about to become a transplant recipient, we might plausibly argue that it behooves her at least to confront her reluctance to think the issue through.

What about the person with squeamish family members? I recommend highly a short story by Richard Seltzer, "Whither Thou Goest," which de-

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picts a young widow who had authorized the donation of her husband's organs, only to become obsessed with the thought that her beloved's heart was still beating away in another man's breast. She was unable to get on with her life until she had tracked down the recipient of her husband's heart and persuaded him to allow her to hear it beating one more time. Perhaps our hypothetical patient has reason to fear that one or more of his loved ones will react in similar fashion. Is that a good reason for his refusal? Do we count that as "won't" or "can't"? It may be helpful to remember that when we are dealing with a living potential kidney donor, we are quite conservative about the risks we will allow them to take, rejecting anyone for whom donation presents a higher than usual risk. Again, we tend to say, "This person can't donate," although the reality is that she could donate, simply at a higher risk.

Finally, moving toward the other end of the won't-can't continuum, consider the person with religious objections to giving but not to receiving organs. Normally, at least if our speech habits are any guide, we think of religious objections as if they were involuntary. We are more likely to hear, "I can't eat at that restaurant, I keep kosher," than "I won't eat at that restaurant, I keep kosher." The reasons for this are complex: for one thing, we tend to think of religious beliefs as irrational—not susceptible to proof and persuasion—and also as inculcated in us by birth and upbringing. For another, we use "can't" rather than "won't" language to signal not true lack of volition, but the pervasive belief in our society that a person ought not to be forced to choose between her religious beliefs and certain basic goods. Thus someone who quits her job because she is a sabbatarian and her plant has moved to a six-day work week is categorized for the purposes of unemployment insurance as being unable to work, as if she had carpal tunnel syndrome or respiratory distress.

The Problem of Foreign Nationals: Test Case for the Free-Rider Argument

Somewhere between "don't" and "can't" we find foreign nationals, those people who come to the United States solely for the purpose of receiving an organ transplant that would not be available to them at home. Since this group has been the focus of much public scrutiny leading to various policy statements, I focus on them as my test case for whether the free rider argument actually works.

The main argument against giving organs to foreign nationals is that, since they are not members of the community which gives organs, it would be unfair to allow them to receive such a scarce resource. At least in theory, every organ given to a foreign national is one organ fewer for Americans who are dying for lack of an adequate supply. There is little or no reciprocity, because Americans rarely go elsewhere in the world to receive transplants.

A free rider is someone who wants something for nothing, who wants to avail herself of a benefit which exists only because others have paid for it. Most systems have enough room at the margin that an occasional free rider does not bring the entire enterprise toppling. For example, a person who sneaks onto a bus without paying is exploiting the fact that most of the passengers have paid, which is what funds the bus in the first place. Absent some mitigating circumstances, we say this person is acting unjustly. Not only is she not bearing the same burden as the other passengers, but over time such behavior drives the costs of the system up, so that other passengers pay even more.

Voluntary and Involuntary Free Riders. Assuming our passenger is able to pay, this seems like the classic example of unjustified free rider behavior—pure stealing. The passenger's behavior is voluntary on both sides: she chooses the benefit of the bus ride, and she chooses not to pay for it. But other examples become more ethically complicated, exhibiting a mix of voluntary and involuntary factors.

When philosophers discuss involuntary free riders, they tend to concentrate on the case of the person who chooses not to pay, but who is the involuntary recipient of an unsought benefit, which involves a distinction between "accepting" (more active) and "receiving" benefits (1). Imagine a group of homeowners who live in a square surrounding a weed-choked, vacant lot—a parable suggested by a somewhat different example in R. Nozick (2). A few energetic yuppies in the group convince the others that it would be worthwhile to contribute some money and elbow-grease to clean up the lot, repair the fence, and plant flowers. This would heighten the homeowners' esthetic enjoyment of their homes, as well as increasing the resale value of their property. But one curmudgeon holds out. Although he has as much time and energy as his neighbors, he does not care about esthetics and plans never to sell his house.

In one scenario, our curmudgeon likes flowers as well as the next person, but simply chooses to put his time and energy into other goods which he values more. In that case, he truly does benefit from his neighbors' sacrifice, unless he covers his eyes and holds his nose each time he passes the garden.

In the other scenario, he is like Oscar the Grouch and prefers the weed-ridden lot, or at least is indifferent to it. If his neighbors go ahead without him, he becomes an involuntary free rider: through no choice of his own, he is the recipient of benefits for which he did not pay his share. (Of course, his free rider status is imposed on him only in a qualified sense. Should he find it ethically abhorrent to be put in that position, he could choose to contribute his share even though he does not want the benefits—"so-called benefits," from his point of view.)

The situation of foreign nationals in need of organs is the exact reverse of the problem of the grouchy curmudgeon. The curmudgeon chooses not to contribute, but has the benefit thrust on him. The foreign national wants the benefit—the donated organ—but through no choice of her own is unable to "pay her share." That is to say, through no choice of hers, she lives in a country which does not have a transplant program. This lack may be due to scarce resources, slow technological development, or, as in Japan, a cultural understanding of the definition of death that does not enable the harvesting of cadaver organs. The foreign national might well prefer not to be a free rider, she might prefer to have been born in a country which had its own transplant program, and she might have supported such a program enthusiastically, but the country of our birth is something we do not choose.

The Concept of Group Membership. The free rider argument should not be used to exclude foreign nationals from receiving organs, because, as I will show, it is based on some unexamined assumptions about group membership. The classic free rider argument focuses on an individual who makes a choice, for example whether to help with the flower garden. The free rider argument in the context of organ transplants, however, focuses on groups rather than individuals, without making a logical argument for how the group is defined.

Arguments against sharing organs with foreign nationals are based on the claim that they are not part of the "giving community." As Prottas puts it:

> It is a sad fact that as long as a shortage of organs continues, some individuals in need must be denied a transplant. Under these circumstances members of the giving community (both American citizens and aliens living in the United States) have a right to expect that their medical needs will be met and that patient selection decisions will not be made to their detriment (3).

Because the argument depends so strongly on the notion of the "giving community," we need to ask why it is defined as all American citizens and resident aliens, rather than in some other fashion. By choosing geography as the limiting criterion, Prottas et al. include some and exclude others without explaining why this is an appropriate choice of boundaries. The answer that leaps to mind is that citizens and residents pay taxes, according to a formula worked out through the democratic process; these taxes form a significant part of the fiscal support of the research and implementation of the transplant process. But the tax argument does not work, because it is agreed by everyone in this debate that foreign nationals must pay their own way.

Money, therefore, is not the criterion of exclusion, because money is something the foreign national can bring with her. The real criterion is the organs. Americans, it is argued, have been donating their organs in acts of generosity and self-sacrifice. "Only the willingness of family members to put aside their own grief can result in the organ retrieval. Every organ transplant starts in tragedy and kindness" (4).

But does American residence automatically define an individual as part of the giving community? A 1985 Gallup poll discovered that 75% of Americans declared themselves willing to donate their organs, but only 17% had actually completed donor cards. A poll commissioned by UNOS in 1987 came up with different statistics: 50% were willing to donate their own organs, and 63% were willing to donate relatives' organs, but only 23% had signed a donor card (5). In other words, even among those Americans without religious or other objections, most people are too indifferent, or too reluctant to confront the thought of their deaths, to take a few minutes to sign their names. Given the easy opportunity (which they can revoke at will) to declare themselves willing, they decline. Why are they members of Prottas' "giving community," while someone from Japan, with no opportunity to give, is excluded?

Since Prottas' definition fails, what unit of society in America could function as the logical equivalent of the individual free rider? The individual transplant candidate herself might be a defensible choice, at least insofar as the person had embraced or rejected the opportunity actively to join the giving community, for example by being a blood or plasma donor, signing a donor card, or working as a blood bank volunteer. In all the discussion of point systems and allocation criteria, I have never seen anyone make this suggestion.

If we balk at making the individual the appropriate unit, perhaps the family is the proper candidate. It used to be common in hospitals for patients to be charged for each unit of blood they used, but those charges were "forgiven" for each unit donated by friends or family in their name. Paul Ramsey suggested something like this when he proposed that "families that shared in premortem giving of organs could share in freely receiving if one of them needs transplant therapy" (6). This idea is appealing, especially if it motivates people to donate. But I doubt that we would want to carry it to its logical conclusion. Imagine a young adult in need of an organ transplant, who was brought up in a religion which objects to donation and who has only recently changed her beliefs. Her friends and family, all adherents to the tradition, have refused to donate, perhaps even preached against it. She has no "credits" built up in her "giving" bank. Although there might be some cynical snickers about "Christian Scientists with appendicitis," would anyone seriously argue that she ought to be disqualified as a transplant candidate? On the contrary, I think most commentators would be quick to point out that one cannot choose one's family, and that one ought not to be penalized for things over which one has no control.

A more difficult version of this question is posed if we contemplate people whose religious beliefs allow them to receive but not to donate organs. Should an American citizen be refused an organ because neither he nor his coreligionists is willing to donate? At first glance, this might appear "fair," but why should one person's religious objection to organ donation preclude her from receiving one, when another person's lazy indifference to signing a donor card is not taken into account?

In fact, there is little or no logical relation between the idea of the "giving community" and the reality of American residency or citizenship. Among the majority of Americans who approve of donation in principle, there is no reason to believe that actual recipients or their families were any more likely to have taken active steps toward supporting the transplant enterprise than the average American. People are assigned to places on the waiting list, there to await their fate, without regard to their status as "givers." The only argument in favor of identifying the giving unit with American residency is that it is nonintrusive (a matter of public record) and conceptually simple, a "bright line rule." But the argument of convenience is not powerful enough to be persuasive in a life-and-death context.

Conclusion

There is a prudential argument for excluding foreign nationals: the fear that Americans will perceive the allocation system as unfair, and the whole system of donation, which is based on generosity and good will, would founder. The evidence for this is ambiguous at best. Where public resentment does exist, it is often based on the belief that foreign nationals have been given preference, or have "bought" their way to the top of the list. There are anecdotal reports of the American public pulling away from donation because of indignation over foreign patients. However, a poll commissioned by UNOS in 1987 discovered that more than half the respondents thought that recipients should be selected on the basis of need; one third felt that U.S. citizens should be treated first. Only 22% were willing to deny organs on the basis of nationality, and that group was selective about which countries were disfavored (7). Thus the case for exclusion rests primarily on a notion of group membership which categorizes the foreign national as a free rider. As I have shown, this is not a defensible position.

Let us look again at the hypothetical "don'ts," "won'ts" and "can'ts" I described at the beginning of this essay. We saw people with religious objections, people who feared that donation might have a deleterious effect on their loved ones, and people who were born in countries without organ programs. Can we seriously argue that these people are less deserving of a shot at life than the large percentage of Americans who say that they are in favor of organ donation, but can't be bothered—or can't face up to inchoate anxieties—to sign a donor card?

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Legal Aspects of the Sale of Organs

Beth Essig, J.D.

With the introduction of transplants the demand for organs has grown and become more compelling. Health care professionals have struggled to find ways to increase the supply of transplantable organs. One of the more frequently discussed options is purchasing them; that is, paying donors for organs.

The legal aspect of the sale of organs is straightforward. Donors of human organs may not be compensated for the donation. In 1984, the National Organ Transplant Act was enacted by Congress (1). This federal statute flatly and clearly prohibits the purchase or sale of any human organ (2). In 1988, the statute was amended to prohibit the sale of fetal organs.

The act prohibits a transfer of a human "organ" in interstate commerce for "valuable consideration." It defines human organs as "kidney, heart, lung, pancreas, bone marrow, cornea, eye, bone, skin or any subpart thereof or any human organ" (3). The statute does permit "reasonable payments associated with" obtaining and processing the organ, including "travel, housing and lost wages incurred by the donor" (4). The statute does not prohibit compensating a blood donor. Most states have parallel statutes.

History of Prohibition of Sale of Organs

Restrictions on the trade in human organs and body parts are premised on the fundamental concept that people (and their next of kin) retain a property interest in their body after their death. Prior to the early 19th century, there was no recognized property interest in the human body, and body parts and human bodies were traded with relative impunity. In fact, the trade in body parts was so brisk in the 19th century that "resurrectionists" roamed the streets harvesting corpses and selling them to schools of surgery. A murder committed by several overzealous resurrectionists to increase their inventory resulted in the British Parliament's enactment of the first comprehensive legislation governing the market in human organs. The law set out two fundamental principles: (a) that bodies and body parts could only be received by legitimate licensed schools for the purpose of training future surgeons; and (b) that it is the family or next of kin which governs the distribution of the body. Modern statutes that address the sale of human body parts still do so on the basis of this framework laid out in the 19th century. The most important aspect of the law is that it recognizes that there is a property interest inherent in a dead body. The recognition of the body as property that can be devised or donated by the individual or controlled by his family is still the law today.

In 1968 the Uniform Anatomical Gift Act (UAGA) was approved by the National Conference of Commissioners on Uniform State Laws an advisory body that develops model legislation which it recommends to the various state legislatures for enactment by the states. Within five years of its approval, virtually every state had enacted a substantially similar statute (5). With the widespread adoption of state statutes modelled on the UAGA, and the federal government's enactment of the National Organ Transplant Act, the current system of donation of organs became firmly entrenched in statutory law. These laws contain essentially the same basic elements as the law that had developed in 19th century En-

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gland. That is, the law (a) restricts who may receive donated organs and (b) recognizes that the donor (and his next of kin) can control whether and how the body parts can be donated.

It is somewhat anomalous that while recognizing a property interest in the human body, the "owner" may not receive compensation for its sale. One of the few recent court cases to consider the question of the property interest of a person in his body is Moore v. Regents of the University of California (6). John Moore, a patient at UCLA, had had his spleen removed. He subsequently learned that tissue from his spleen had been used to develop a cell line of some commercial value. Mr. Moore, considering himself the owner of his body, asserted that he was entitled to financial compensation. Indeed, the trial court determined that Mr. Moore had a "property interest" in the cell line and ordered that he be compensated. This decision was reversed by the California Supreme Court, which determined that, assuming that appropriate consent had been obtained from Mr. Moore for the use of his spleen for research purposes, he did not retain ownership interest after the removal of the organ and was not entitled to compensation.

The Current Debate

One of the most significant issues for professionals involved in transplants is how to increase the supply of organs. In that context, numerous proposals have been made. These options are discussed in other articles in this symposium. They include offering compensation to the estate of the donor, or to the living donor, for the purchase of the organs.

Proponents of permitting the sale of human organs argue that a free market in organs would increase the supply. They further argue that, inasmuch as the body is recognized "property" that is controlled by the individual, it is paternalistic to prevent the body's "owner" from seeking compensation in the event of an organ donation.

On the other hand, permitting commerce in human organs raises numerous troubling issues. The question in this era of transplants is, can we afford to ignore any solution that might lead to an increase in organ availability and an increase in the number of lives saved through transplants?

There is a concern that the availability of compensation for organ donors would exploit the poorest and most vulnerable members of society and pressure them inappropriately to contribute their organs. This view holds that compensation interferes with "voluntariness," and that organ donors, especially live donors, who agree to donate their organs for money will be unduly influenced by the availability of compensation. This concern is visible as well in other areas of medicine where compensation for nontherapeutic health care or anything that interferes with an individual's bodily integrity is restricted or prohibited, for example, in the well-accepted principle that a payment to induce a research subject's participation in a protocol is inconsistent with the voluntariness of the informed consent process for human subjects.

The view that payment for the donation of the body interferes with "voluntariness" also underlies the recent spate of legislation and case law which prohibits the payment of money to "surrogate mothers" or which makes agreement for payments to surrogate mothers unenforceable. The position taken by some in that debate is that the payment is unduly coercive and will induce women to make decisions to become surrogate mothers solely for economic advantage.

Conclusion

The view that donors should not be compensated is deeply ingrained in our legal tradition. Nonetheless, the need for organs to save lives may lead to a reexamination of that view and a relaxation of the current prohibition under appropriately regulated circumstances.

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Markets and Morals:

The Case for Organ Sales

Gerald Dworkin, Ph.D.

Arthur Caplan has said that "perhaps the most pressing policy issue facing those within and outside of the field [of organ transplantation] concerns the shortage of organs available for transplantation to those with end-stage organ failure" (1). The options available to increase the supply of scarce goods are basically three—donation, conscription, or sale. A good deal of attention has been focused on the first two methods (I take presumed consent to be basically conscription with an option to opt out before death), but the sale of organs has been little discussed.

I focus on the issue of whether there are good arguments of an ethical nature which rule out a market in organs. I leave to one side discussion of whether such markets would in fact increase the supply of organs, whether there are practical difficulties in the implementation of such a scheme, whether political considerations (in the broad sense) would make it difficult to gain support for such a system. My only task today is to assess the moral arguments.

The first distinction we must make is between a futures market and a current market—that is, between the decision of an individual to sell the right to his organs after his death, and the decision to sell organs while he is alive. I assume, for the sake of this discussion, that if there are moral objections to the sale of organs they will take their strongest form against the sale of organs from living donors. Hence if one can show that there are no conclusive arguments against such sales, one will have shown, ipso facto, that there are no conclusive objections against the sale of cadaver organs.

I first briefly consider the arguments in favor of a market in organs and claim that in the absence of moral objections, there is no reason for not having such markets. I then want to consider all the plausible arguments against the sale of organs and show that they are not legitimate objections. My conclusion will be that, in the absence of further arguments which survive critical scrutiny, there are good reasons for favoring a market in organs.

Arguments for a Market

We currently accept the legitimacy of noncommercial solid-organ donations. We also accept the legitimacy of the sale of blood, semen, ova, hair, and tissue. By doing so we accept the idea that individuals have the right to dispose of their organs and other bodily parts if they so choose. By recognizing such a right we respect the bodily autonomy of individuals, that is their capacity to make choices about how their body is to be treated by others. By recognizing such a right we also produce good consequences for others, that is, save lives, allow infertile couples to have children, further medical research, and so on. But the primary good achieved by such a right is the recognition of the individual as sovereign over his own body. A market transaction is one species of the larger class of voluntary transactions. Allowing people to sell things is one way of recognizing their sphere of control.

Finally, by allowing individuals to either barter or sell something, we increase their level of well-being. Since such transactions are voluntary, they are presumably only engaged in when the individual believes himself or herself better off without the good and with the cash (or an al-

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ternative good in the case of barter) than without the cash and with the good.

So markets can increase both autonomy and well-being.

Arguments Against a Market

There are often compelling reasons why we should not allow individuals to sell what they could give. We do not allow markets in votes, in babies, in judicial decisions, in college grades. In these cases we recognize countervailing considerations which are sufficient to overrule the considerations in favor of markets. So the question before us is whether there are such counterarguments in the case of markets for human organs. I propose to consider the arguments that have been adduced and show that they are not compelling.

Exploitation of the Poor. One of the most powerful arguments against a market in organs is the element of exploitation of the poor. Clearly, those who are most likely to wish to sell their organs are those whose financial situation is most desperate. Those who have alternative sources of income are not likely to choose an option which entails some health risk, some disfigurement, some pain and discomfort. The risks of such sales will certainly fall disproportionately by income class.

But what exactly is supposed to follow from these facts? Is it that, because of this, the choices of the poor are not, in fact, fully voluntary? This seems to me false. Or if it is true, it has a much wider implication than that organs should not be sold. It suggests that poor people should not be allowed to enter the army, to engage in hazardous occupations such as high-steel construction, to become paid subjects for medical experimentation. There are certainly objections of justice to the current highly unequal income distribution. But it seems to me paternalistic in the extreme, given that injustice, to deny poor people choices which they perceive as increasing their well-being.

Here it is important to have some idea of the size of the risk we are talking about. One study has estimated that the increased risk of death to a 35-year-old from giving up one kidney is roughly the same as that associated with driving a car to work 16 miles a day (2). Imagine saying to a poor person either that her choice to commute such a distance is not voluntary, or that if it is, she still ought not to be allowed to commute such a distance, although we will allow middle-class persons to do so.

To make this point more vivid, what would your reaction be to the following proposal made by one author in response to this objection? Prohibit purchases from individuals whose average income is less than 80% of median family income. This has the effect of removing persons in the lower 40% of the income distribution from the market (3). Would you now be more, or less, inclined to favor organ sales?

Note also in the context of arguments about justice that the poor are disproportionately represented among those who need transplants. Thus, assuming—as is currently the case—that the government subsidizes most organ transplants, they stand to gain as a class more than the rich.

Another objection based on the fact of income inequality is that because of unequal bargaining power the price paid to the poor will not be a fair one. They will not get the full market value of their organs. If there were evidence that this was true, the solution would be to regulate the market, not forbid the sale. One could establish minimum prices analogous to minimum wage laws.

Distributional Consequences. If organs are for sale to the highest bidder, the rich will get them and the poor will not.

First, this seems an objection not to the sale of organs but to the general system of medical care based on ability to pay. There are currently at least 50 different types of artificial body parts which are distributed according to ability to pay. Why is it better for the rich to have better access to artificial than to human kidneys?

Second, currently, few individuals pay for transplants out of their own funds. Most transplants are paid for by public and private insurance. So the issue again is access to health insurance, not access to organs.

Note also that the main costs associated with transplants are likely to remain the fees of doctors and hospitals and the costs of drugs, all determined by markets. Why is it legitimate for these to be the results of markets and not the organs themselves?

But if one finds that the distributional implications are unsatisfactory, regulations or restriction on sales are called for. We could adopt a scheme, for example, in which it would be illegal for private individuals to sell organs to other private individuals. They could only sell them to the state. The state then could adopt whatever scheme of distribution would ensure justice in transfer—perhaps a lottery among the equally medically needy, or a first-come, first-served principle.

Irreversibility. One objection to the sale of organs, as opposed to renewable tissues such as blood or semen, is that the decision is irreversible.

Individuals may come to regret the fact that they have sold a kidney—particularly if they develop kidney problems with the remaining organ. But we currently allow individuals to make many permanent changes in their body, including breast diminishment and sterilization. If we feel the problem is more severe we can establish waiting periods, counselling, and so forth.

More Choices Not Always Better. The argument that more choices are not always better says that allowing new options does not leave the old options unaltered. Applied to the sale of organs, the claim is that once a market price is established for organs, individuals who choose not to sell do so in the knowledge that they have made a choice which leaves their family worse off economically than they might have been. Individuals are choosing to decline an option which they formerly did not have. They may be psychically worse off than if they never had such a choice. I agree that this is a cost. I do not see, however, that it is anywhere near the psychic costs that are incurred by individuals and their families who face blindness and death as a result of an inadequate supply of organs.

Another psychic cost is more significant, as Hansman argues (3). If one assumes that because of tissue matches, the most efficient donations are from family members, it is likely that introducing markets is liable to strain family relations. Family members are likely to be resentful of being asked to contribute without compensation when a stranger would receive substantial payment. It seems, however, that the rapid development of immunosuppressive drugs may considerably weaken the first premise of this argument.

Commodification. Finally we come to a large class of arguments which object to the commodification of organs. These arguments are rather diverse in character—many are discussed by Radin (4)—and one has to examine them carefully to see how they differ and whether any of them have sufficient force to overcome the presumption in favor of allowing sales of organs.

Altered Nature of the Transaction. Peter Singer, in a well-known argument against the sale of blood which would carry over to the sale of organs, claims that the nature of giving changes when blood is allowed to be sold as well as donated:

> If blood is a commodity with a price, to give blood means merely to save someone money. Blood has a cash value of a certain number of dollars, and the importance of the gift will vary with the wealth of the recipient. If blood cannot be bought, however, the gift's value depends upon the need of the recipient (5).

There are actually two arguments here. The first is that the sale of blood means that the significance of the transfer will vary with the wealth rather than the need of the recipient. Unfortunately this argument is much too powerful, since it is an argument against the sale of anything. Why distinguish blood from food?

The second argument has more weight. It is that if one adds to the existing practice of donation the use of a market, the situation for donors is altered. Whereas before they were able to give something that could not also be purchased, now they can only give something that has a price as well. The nature of their gift is changed. Although I concede that this is true, I do not see it as a compelling objection to allowing such sales. Donors do not have the right to have their gift retain its special character, and if the price of so doing is that potential recipients of life-saving resources are excluded from receiving them (because the supply of donations is limited), the consequences alone would argue for not forbidding such sales.

Alienation. Charles Fried argues that:

> When a man sells his body he does not sell what is his, he sells himself. What is disturbing, therefore, about selling human tissue is that the seller treats his body as a foreign object . . . the shame of selling one's body is just that one splits apart an entity one knows should not be so split (6).

Notice first that this argument (similar to one given by Kant) applies to the sale of blood and semen as well as organs. So if this argument is good, it shows that our current policies are illegitimate. (Although Fried seems to take it back in a footnote [6, p. 143] saying that the selling of blood is "personally bad . . . though not in any sense wrong.")

But the main objection to this argument is that it implies not only that the sale of blood or hair is bad, but also that the donation of such bodily parts is bad as well. For if selling organs splits apart an entity one knows should not be so split, so does donating it. One treats one's body just as much as a foreign object if one gives away a kidney as if one sells it.

The danger we want to avoid at almost all cost is that people start to be treated as property by others. But this is avoided by leaving all decisions about their organs, tissues, and so on to the persons themselves, and insuring that their decisions are voluntary.

Driving Out Altruism. The argument about driving out altruism is that allowing a market in some item will make it less likely that those who were inclined to give on altruistic grounds will continue to do so. The data on blood are ambiguous on this point—some tending to show such an effect, some not. It is clear, however, that the presence of markets does not generally drive out altruistic motives. Most hospital workers are paid, but there are still volunteer workers. There are markets for used clothing, but many people give their used clothing to the needy. Lawyers are paid for their services, but many contribute a portion of their time pro bono. Finally, even if it were true that a market in organs would somewhat reduce the number of people who donate organs, if the total supply is increased, one has to weigh the loss of altruism against the gain in human lives. I see no reason to suppose that the balance will be negative. After all, we allow a commercial market for caregivers for our elderly parents—surely an arena in which not only generalized altruism but debts of gratitude play an important role.

Conclusions

It seems to me that if we take into account all the welfare losses that will accrue because of the introduction of markets for organs, it will still be the case that if the supply of such organs is significantly increased, the two major gains in welfare (improved health and decreased mortality, and increased income for sellers) will significantly outweigh the losses. If there are no nonconsequentialist considerations (such as denials of rights or considerations of justice) which might trump such consequentialist considerations, the consequences ought to be determining.

My conclusion is that, absent other and stronger arguments than those considered, given that both rights and welfare argue in favor of a market for living organ donations, there is no reason not to allow them. In addition, whatever the force of these objections, most of them are considerably weaker when applied to the sale of future rights in cadaver organs. So such a scheme is, I believe, certainly warranted.

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Getting and Giving:

Panel Discussion

Moderator: Rosamond Rhodes, Ph.D.

Lewis Burrows: I would like to review some remarks I made at a recent meeting, "Justice, Commerce, and Ethics in Transplantation," sponsored by the Canadian government and the American and Canadian transplant societies. At that meeting members of the clergy took a strong stand against both selling organs and versions of "rewarded giving," apparently because of belief that human beings are intrinsically good and therefore, given the opportunity to be altruistic, they will be. Unfortunately, as we have learned at this conference, there is an increasing need for cadaver organs which is not being met. Someone has commented here that the only group asked to be altruistic is the recipient's family. Certainly hospitals profit greatly from transplantation. Physicians and transplant professionals who earn their living by or advance their careers through transplantation profit greatly. The medical-industrial complex and the drug companies make huge amounts of money through transplantation. Even the government profits when patients no longer need dialysis. I cannot see anything wrong with the concept of rewarded giving, at least as an interim measure until we can improve our ability to attract donors, provided that the distribution be either through government or paragovernmental agencies to insure that no commercialization is involved in the distribution.

Robert M. Arnold: It seems to me that those of us who deal with organ donations and procurement need to stop going from one failed policy to another and spend more time trying to figure out why the policies have failed. In the early 1980s the claim was that people wanted to give and the problem was that doctors didn't ask often enough. If we would only ask, more people would give. However, with increased requests we didn't get the increase in donations that everybody thought we were going to have. Now the movement is to either pay people for giving or create a futures market. I am of the mind that there aren't nonconsequential arguments for not having a market. But I am not sure that throwing money at the problem is going to solve it. We ought to begin to do some small-scale studies to figure out why people give, and what things will increase giving. It may be that giving would increase if only people from organ procurement organizations asked.

Bernard Baumrin: I'll throw my two cents in. I think a cheaper, easier, and more effective solution would be, if you don't give you don't get. People who don't sign up can't get organ transplants.

Charles Miller: That's a possibility. You would join the donor community in order to be a recipient in the same community. But the logistics would be difficult, and the education is so fraught with error that it may not be practical.

Burrows: Only a very small percentage of people ever need a transplant. There are only 25,000 people in the United States today who need a transplant. You may extend the indications in the year 2,000, but as of now the vast majority of people just would take the chance of not signing a donor card because they'll probably never need a transplant.

Miller: We had 4,000 organ donors last year and the year before; 25,000 patients are on the recipient list now. The average rate of consent in the United States has been around 50%.

Adapted from a panel discussion at the conference "Transplantation: Ethics and Organ Procurement" at the Mount Sinai Medical Center on March 13, 1992. Address reprint requests to the moderator, Director of Bioethics Education, Mount Sinai School of Medicine, Box 1193, One Gustave L. Levy Place, New York, NY 10029.

Arnold: The refusal rate varies. In an Ohio Department of Health study the refusal rate was 70%. In a New Jersey study the refusal rate was 60%.

Miller: Sales or financial incentives might make the donation rate go down. It could create a backlash against altruism. And so I agree that a pilot study of these ideas should be done to see exactly what does happen to the consent rate.

Arnold: In 22 hospitals in Pittsburgh and Minnesota we are reviewing every patient who dies in the hospital who is eligible to donate organs, tissues, or corneas. We're interviewing all health care professionals associated with those patients' deaths and asking if they identified the patients as eligible, whether they talked to the families, what the professional said, and what the family said. A year into the study, a rough look at the data indicates that, in fact, health care professionals do a good job of identifying organ and tissue donors. The major reason for failure in procurement is that families say no. In our planned followup study we are going to interview families to try to find out why families are saying no. With that information you can try to set up intervention.

Dena S. Davis: I think a lot of people don't sign donor cards because they're afraid that doctors will let them die too soon. This is ironic because people also fear that doctors won't let them die soon enough. People don't trust that the medical community is communicating with them.

Beth Essig: Every year more and more countries seem to be moving toward a policy of presumed consent.

Arnold: But no one's done a good empirical study on whether doctors and the organ procurement organizations really practice presumed consent. Arthur Caplan tells stories about France where they have presumed consent but people don't follow it. People still ask families, and when families say no they don't take the organs. In Austria this doesn't occur, but Austria has a long tradition of using dead bodies for state purposes. In fact, one of the things that's interesting about Austria is that when they passed the presumed consent law there was no opposition.

Burrows: In the United States last year there were roughly 4,000 donations, and the average consent rate in most states was 50%. That means we were turned down by about 4,000 families. But we've estimated that somewhere between 14,000 and 20,000 individuals are already awaiting organ donations. This leads us to the issue of the paid living unrelated donor. Nobody seems to want to bring that up because the inherent classism is abhorrent to us. But we should remember that it wasn't the rich kids who fought in the battle fields of Vietnam, it was the poor kids. The risks there were greater than the risks of giving a kidney. So the precedent has been set to some degree. We have been willing to tell a certain segment of our population, "You can go out and fight for us and take great risk with your lives in Vietnam." But to date we're unwilling to take that same segment of the population, that desperately poor population, and say to them, "If you want to give up one kidney where the risk is very small and get paid for doing it, you can do it. It's against the law to do it." We did it again in Iraq. We said it was unfair in Vietnam and yet who did we send to Iraq? We didn't conscript college kids.

Miller: I have been thinking about some of the comments Prof. Dworkin made. He was wondering why it was any different to sell an organ than it might be to do any service or sell anything else. There are actually some qualitative differences. First, selling a body part is somewhat extraordinary. And it may not be possible to really give somebody information about what the risk is. Maybe for kidneys it is, but probably for the liver it is not. Second, it's not something you can do over and over again. You can only do it once. I am not sure that rules it out, but it does make for a difference. Do you have a right to sell a vital body part?

Dworkin: I am not sure that we are not able to get reliable estimates of the risks. If that's true, why doesn't that count as much against allowing people to donate as allowing them to sell? Presumably you want to obtain informed consent in both cases. Presumably in both cases you want the decision to be as fully voluntary as it can be. How does the addition of monetary compensation affect the question of informed consent?

Miller: It adds a bit of financial coercion, and where there's a degree of uncertainty about how reliably you can inform somebody, any addition of coercion becomes all the more problematic.

Dworkin: But then, presumably, something of the same worry arises, for example, with siblings and the emotional coercion that goes with family.

Miller: Absolutely.

Burrows: I want to tell a true story which may illustrate some of the things I have been trying to say. About ten or twelve years ago I was approached by a well-known Indian nephrologist who had trained here at Mount Sinai and who then ran a large dialysis program in Bombay. In India, of course, only the wealthy are dialyzed. It's not universal, as in this country. He was offering me the opportunity to transplant wealthy

Indians who would come to Mount Sinai along with their donors, who were being paid a considerable amount of money in Indian terms. He was hoping to use a major American center for the best of medical care, to provide the donors with the smallest risk and the recipients with the best opportunity for success. All of the donor's medical care would be taken care of by the recipient. And I turned him down cold.

I turned him down primarily because it was a matter of using the desperately poor in what amounted to a bidding war by the rich. The method of distribution was not fair. The Indian nephrologist got upset and asked if I had any idea what that money would offer to the poor Indian peasant; did I realize how it would change not only his life but the lives of his children? The seller would be able to have a dowry for his daughters, he would be able to buy a piece of land for his sons, he would be able to send his children to the university. We still turned him down, and I don't think Mount Sinai would have accepted my participation either. He was using the desperately poor to serve the desperately sick rich.

Question: I know we won our victory over the Soviet Union, but that doesn't imply that everything is marketable. You argued that maybe you can sell part of yourself but, would that be morally right?

Dworkin: To make my position clear: I never argued that all things should be for sale. In fact, I gave several examples of things that I thought should not be for sale: votes, judicial decisions, and grades. In each case I should hope I would be able to provide you with some kind of principled reason as to why I wanted to distinguish those cases from other cases. Now it seems to me that the case you give is a perfectly reasonable one. I don't think we should allow people to simply exercise arbitrary power over one another and force them to degrade themselves and sell their hair, for example. Some of you may know the play by Durenmatt, *The Visit,* in which a woman comes back to town who early in life was badly treated by the villagers in her town. She wants to see how much it takes to make each of these people do some terrible thing. The question simply was how much of a price each individual would exact. I would certainly be opposed to allowing people to offer large sums of money so that people could mutilate themselves arbitrarily, but this case seems quite different—no important social good was served. I am assuming that organ donation will, in fact, save people from dying, allow people to see who otherwise wouldn't see, and so forth, and so donation offers some important social good. It seems to me that once this has been established, and if you accept some kind of an initial presumption that people should have a righ to control their bodies, you require a strong argument to prevent the sale of a body part.

Question: What about looking at whether the recipient has certain rights to a transplant? Do ou social policies infringe on those rights?

Dworkin: At most what could be shown is tha you do have a right to a certain institutionalize system of medical care, and that may include right to be placed on a list under certain conditions. But you certainly don't have an individualized right against the other particular person That's clear. And unless you believe that som system of conscription is legitimate, I don't thin you even have a generalized right that somebod or other provide you with an organ.

Rhodes: We usually think people have at least right to try to get what they need. They may no have a right to what they need, but they at leas have a right to try to get it. But here the government says no, you can't try to get the transplan which you need.

Essig: If society decides that procuring organs fo people who need transplants is more importan than letting people be buried with all of thei body parts, things would work differently. A lot o the things we have talked about are alternatives We have talked about cadaver organs, but th dead do not have the same right as the living What we are talking about is the right to tak organs from dead people.

Arnold: I am not sure how this right would apply It would be like people saying, "There isn' enough food around and yet the farmers aren' using every inch of the farmland to grow food Since I have a right to get what I need and I nee food, I should be able to force the farmer to use th rest of the farmland to grow food." I don't understand.

Rhodes: She's saying we all have a right to try t get food. If we were allowed to buy food, th farmer would have an incentive for growin more.

Baumrin: If someone was withholding land fron tillage for some reason and there were actuall people starving, the government would be entitled to interfere on their behalf in expropriatin land from the individual who kept the tillabl land out of production.

Arnold: The government might be able to do that although there might be countervailing reasons What the government needs to say in this case i look, you have a right to try to get what you want If there were no countervailing reasons not to al low people to sell organs, we would let them sell organs. But, in fact, we think there are countervailing reasons. Then the question is, are the countervailing reasons consistent with societal policy? And then we're back to the fireplug.

Essig: The first time Congress made clear that you couldn't sell organs in interstate commerce was in 1986. The only state I know of that now has a statute permitting sales is Mississippi; previously there were more states with statutes permitting organ sales. There are states with no statutes where there have been sales, such as California. Currently, the movement everywhere is to prohibit sales.

Question: The distinguishing characteristic of what you can rightly sell is rightful ownership. For instance, you shouldn't be able to sell children, because you don't own children. You shouldn't be able to sell grades, because a grade is something the professor controls, but doesn't own. If you rightly own it, you ought to able to rightly sell it. And I can't see a better case for ownership than for a body part. But there's another factor besides superstition that is operating against allowing markets in organs. Technologies tend to inherit the politics of the era that they're born into. Over the past century in the developed world, there has been a general trend toward increasing authoritarianism and greater antipathy towards freedom of individuals and markets. Later technologies have come under tighter restrictions.

Dworkin: I am not inclined to accept that principle that whatever you legitimately own you may legitimately sell. In particular, for example, I have grave doubts about whether you should be allowed to sell your heart. And I think you own your heart as much as you own your fingernails. So I think there are other considerations that enter; that principle is probably too strong.

Burrows: The donor should have his own advocate. As the transplant surgeon, I can't be the advocate of both donor and recipient because I have a conflict of interest there. The donor should have somebody to advise him, to help him. In the case of the under-age donor that Dr. Rhodes discussed, we tried very hard to find an advocate for the donor other than ourselves or the pediatricians who were caring for the recipient. The court ultimately became his advocate. We had to make him a ward of the court. Obviously there is a conflict under any circumstance, even in cadaveric transplantation. We no longer care for the cadaveric donor in his agonal phase. That is now done by individuals who are not in any way advocates of the recipient.

Question: Can any surgeon who is to economically benefit from performing the surgery ethically remove an organ from a living donor for transplant into another?

Miller: We feel justified in doing living-related transplants because they involve an altruistic gift to a close loved one. This is a donation you can only give once. And, as surgeons, we're pretty well assured that it is given at the best time and for the best reason. I am assured that the recipient will derive a benefit from the donor's risk. In a free commercial market, the donation might be more valuable next week. The price of the organ may go up. Possibly the donor should wait a week to get the greatest benefit from donation. I could not be certain that he was receiving his fair share of the deal, so I wouldn't feel comfortable doing it.

Dworkin: Your worries about the distributional consequences of organ sales call for regulation of the market. In Dr. Burrows's system, organs should be sold only to the state to assure fair distribution.

Burrows: Transplantation is difficult and different from anything else in medicine. I am not saying that because I'm a transplanter. We're not giving a piece of plastic—a heart valve, or a pump, or whatever—to the receiver who will receive it. It's the giving of a vital living organ to another individual, and it takes a giver and a receiver, and that's why all these ethical issues are arising in transplantation. The thing we are trying to work out is a system to maximize giving along ethical lines.

Arnold: But selling organs could be wrong for another reason. If I am your friend I might come to your house and do things for free because I really like you and you're a really good person. After I come over you could say, "Here's $10 for your trouble." That $10 doesn't add something to our relationship. I may be upset with you because you are no longer letting me be altruistic.

Baumrin: Okay, so he'll be miffed with the medical community. Is there anything besides his being miffed that makes it wrong? Some won't be miffed. Some will be very happy. I was touched that Dr. Burrows would turn down the Indian peasant who had one chance at bliss by selling his kidney. But he was enforcing our view of the world on the Indian peasant.

Davis: Actually, if you brought the Indian donor to this country you would have done a lot of good. The Indians who sell their organs in India are not having the kind of good consequences that American organ donors have because they are not necessarily in as good health, they're not as carefully chosen, and they live much more difficult lives. The way it works now, it really hasn't been the benefit to the poor Indian donors that one might have expected.

Arnold: Stewart Younger has a wonderful article in *Transplant Proceedings*, "The Dark Side of Organ Donation." What he basically says is that everybody loves organ transplantation. If you ask the public about it, 99% say they're in favor of it. But nobody likes thinking about organ procurement. There's a long history of being afraid of things happening to the dead. It will take some time to have those superstitions, fears, or whatever drives those fears come to the surface and be worked through. There's a real worry that if it's pushed too fast, we will basically get the backlash of those fears and heighten them.

Question: The medical examiner may perform an autopsy over the objection of the family. If that law was somehow acceptable in our society, perhaps presumed consent could also be accepted.

Arnold: That's also true for corneas. In many states there are presumed consent laws for corneal donations. I don't know how those laws got passed. But we've been trying to see if there's a unique legislative history to passing those laws. There has been some case law involving families that protested when the corneas were taken without coming to the family to get consent. Courts have upheld those laws. Yet, for at least the near future, there will be nowhere near enough implantable organs for the people who would benefit from them.

General Articles

A Hospital Experience

David Z. Starr, M.D.

Abstract

This article is an account of the author's experience and observations on having been incorrectly diagnosed as having a myocardial infarction and having been admitted to a coronary intensive care unit. The article touches on the rigidities of medical thinking, how one can come to believe what is not true, how to be an "exceptional patient," how medical care feels from the other side, and other relevant observations.

I recently had a medical experience that, although certainly not unique, is something many physicians do not have until later in life, if at all—an experience whose lessons should be continually impressed on all physicians. At the age of 43 and slightly overweight, I was admitted to a coronary intensive care unit because my electrocardiogram seemed to indicate I might be having a myocardial infarction. After five days in two coronary intensive care units, in which I was treated as if I had had a myocardial infarction, three additional days on a cardiac ward, a cardiac catheterization (which was normal), and a stress test, it was determined that I had no cardiac disease, although my cardiogram was somewhat unusual for other reasons. The medical conclusion was that I had had a muscle pull from some vigorous karate exercises I had done four days prior to admission to the hospital.

My theme in this paper, however, is not to inveigh about the vagaries or misdiagnoses of modern medical practice. Given the chest pain and cardiographic abnormality, which could not be compared to any other previous cardiogram, the admission was most likely the correct thing to do. However, I am a psychiatrist and I believe several observations of what happened to me would be helpful to those engaged in the practice of medicine.

My observations fall into two categories, one related to doctors and how they think and the other to how I felt and was treated as a patient.

How Physicians Think

The most striking observation about how doctors think is the tendency to categorize and then to continue to operate in accord with the original categorization. Although my chest pain was atypical for coronary occlusion (it came on at rest while I was listening to patients, continued for seven or eight hours, and was not crushing or severe or made worse by exertion), once the cardiogram was read as possible myocardial infarction, the details regarding the vigorous arm movements in karate, about which I had told my doctors, were lost. Even when the laboratory reported that the cardiac fraction of the serum creatine phosphokinase (CPK) level was normal, the next diagnosis that was entertained was unstable angina (the laboratory did report that the total CPK level in the serum was elevated). Nonetheless, people kept thinking "heart," and everything was read in this light. I was dealing with heart specialists, and heart specialists deal with hearts and think "heart." One doctor, without even getting all the details, said I probably did have a myocardial infarction. Only when the cardiac catheterization was found to be normal did people begin to step back.

I say this not so much to condemn as to remind us that we all, to some extent, think in cat-

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egories and tend to generalize from a fixed position. We have to be careful to always reevaluate a diagnosis and not think rigidly. Incidentally, I live in Boston, and the hospitals involved were both university affiliated, one being a rather prominent hospital affiliated with a prestigious Boston medical school.

How Patients Respond

However, the more profound observations came from my role as patient. On the positive side, I think the physicians extended themselves to make sure nothing was wrong because I too was a physician. However, in their zeal to let me know I now was a patient and not in control, they kept me alarmingly in the dark about the technical aspects of my case. No one had enough time to show me anything. For example, no one showed me my cardiogram until I begged it out of the intern on the night before I was going home, after everything was determined to be all right—this despite the fact that the cardiogram was the primary reason for the misdiagnosis, and all the tests had been based on this technical item.

Although obviously a sick physician cannot be his or her own doctor, I think there is an art to accepting the fact that a physician may need or want to know more and that there has to be a balance between this desire for technical information and the physician's role as a patient. I think Aristotle's Golden Mean should be the rule here. Neither the role of being purely a patient nor letting the physician control his or her own treatment works well. The art lies in balancing the two, so that some knowledge can be given while ensuring that the doctor remains a patient.

Another observation I made as a patient is that it is amazing how easy it is to be persuaded that you are sick even if you are not. In telling me that I probably had cardiac disease and treating me as if I did, replete with all the instrumentation, nurses, drugs, and so forth, the doctors convinced me for a period that I did have cardiac disease—so much so that when the first doctor I saw after the catheterization told me I might not have any cardiac disease, I did not believe him. I thought he was wrong. After all, the doctor who saw me earlier in the day told me I probably had had a myocardial infarction and he had scared me into possibly believing him.

It never fails to amaze me how the power of words and statements from persons in authority can convince people of things that may not be true. Although I really was not sick, the caregivers made me feel I was sick, complete with side effects from the medications they were giving me (for example, headache from the nitroglycerine, which forced me to ask for more medication to reduce the headache). We all live to a great extent in our minds, and each of us can be persuaded of things that are not true, given enough props, regardless of our intelligence or sophistication.

The Exceptional Patient. Still another observation I made as patient was that to keep my sanity and not be overwhelmed by what everyone was doing to me, I had to fight the system to some extent by not accepting the myriad contradictory rules of the cardiac intensive care unit and by questioning each new drug I was to receive without even being asked. I had to be what I later discovered, when reading Bernard Siegel's excellent book *Love, Medicine, and Miracles* (1), is the "exceptional" patient.

By exceptional patients Siegel means those who fight back, who fight the system, who do not passively accept their disease or condition, but who want to know everything that is going on and to be actively involved in the fight. Siegel, who is a surgeon who treats many cancer patients and who has gotten involved with the psychologic aspect of illness, divides his ill (usually cancer) patients into three types:

- those who, either consciously or unconsciously, want to die to escape the pain of their lives and/or their illness and who seem to actively undermine and fight treatment (about 15%–20%)
- the middle of the spectrum—patients who are compliant and do what the doctor wants (take their medicine, keep appointments) but tend to remain passive, expecting the doctor to do the work; physicians often like these patients because they are compliant and do not challenge them (60%–70% of the patients)
- "exceptional" patients—those who actively try to fight their disease, who want to know the results of all their laboratory tests, who will challenge their doctors, who will look into alternate treatments on their own, who are often considered difficult patients (15%–20%). For example, Siegel quotes studies to show that long-term survival is greater in cancer patients who are judged difficult by their physicians. That is, they challenge the physicians, they feel, they get depressed about their illness, they fight back, they are not stoic.

I found these facts to be true on my own, before I read Siegel. If you do not fight back to some extent when fighting back is appropriate, I think you become even more of a victim. I think this ability to keep some control is what allowed me not to be traumatized by the whole experience and what sometimes allows even sicker patients, as Siegel has observed (1), to keep on living and improving, even at times with cancer.

How Caregivers Act

I leave two of what I believe are my most worthwhile observations for last. These have to do with the twin "k" words: competence and kindness, the two qualities that affected me most during my stay. When I was most frightened and in danger—when I was told that I might be having a heart attack—I was most reassured by those who appeared to be competent, who seemed to know what they were doing, and who seemed also to care about me. I homed in on this quality the way a drowning person grabs a log. It is a quality that some caregivers have and that amazingly large numbers do not. When you are scared, you can pick up the difference in a second.

As to kindness, it is a trait we easily forget about in our pressured, high-technology practices. But when you are lying in a cardiac intensive care unit at the mercy of your doctors' and nurses' orientations and whims, believe me—how kind and flexible they are really counts.

Some nurses showed extra flexibility and care, even when it meant, say, getting one less measurement of my blood pressure in the middle of the night. Among the nurses, I think the lack of kindness often came out as overrigidity with rules and, in some cases, covert sadism that one could sense. These nurses were more involved with following the rules than really caring for the patient.

As to the physicians, some, despite their busyness, also showed an extra bit of kindness and empathy. But many did not. Among the doctors, the lack of kindness often came out as a coldness, a technical, nonempathic aloofness that, even if he or she was right, tended to demean me and make me feel degraded. The patient can easily pick up what the doctor's attitude to the patient is, and it makes a big difference.

Perhaps one of the biggest lessons I learned is that even in our rushed and busy professional lives, an extra moment of kindness and caring is felt and appreciated by those on the other end. We should never forget this. Above all, I learned this: Always keep an open mind and question your diagnoses. No matter how good you are or think you are, you will sometimes be wrong.

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Equality, Justice, and Liberty
America's Unfinished Agenda

FAYE WATTLETON

IN THE mid-19th century, a young man sent his manuscript of poetry to a man he greatly admired, Ralph Waldo Emerson. Mr. Emerson read the work, called *Leaves of Grass,* and wrote back to Walt Whitman, "I greet you at the beginning of a great career."

And so I greet you, the graduates of Mount Sinai School of Medicine, Class of 1992, at the beginning of your great careers. By now, you may think you've had your fill of "good advice," but I hope you will consider one more bit of advice.

As you pursue your interest in preserving the health of Americans, I urge you to always keep your eyes on the bigger picture of life—a concept illustrated by a story about former Yankee manager Yogi Berra. It seems that one day in Yankee Stadium, back when streaking was the fad, two people jumped out of the bleachers stark naked and rounded all the bases. When Yogi got home, he told his wife about it, and she asked: "Were they boys or girls?" Yogi said, "I don't know, they had bags over their heads."

Yogi missed the bigger picture. And if we fail to see the bigger picture, we will not comprehend the vast array of forces aligned against Americans' fundamental rights. The bigger picture is that after 12 years of the New Right agenda and the systematic reconstruction of the federal courts, much that Americans have taken for granted is being dismantled.

The Bush administration's gag rule tells doctors what they can and cannot say to women. In *Planned Parenthood of Southeastern Pennsylvania v. Casey,* the Supreme Court may rule that doctors become government propagandists; that women endure waiting periods and husband notification; and that teenagers obtain parental consent before getting abortions. The invasion of the doctor-patient relationship is a natural extension of the invasion of women's fundamental rights. The bigger picture is that both the gag rule and the Pennsylvania law are attempts to wrest from women the power to control our reproduction. The widening circle of oppression that now encroaches on our first liberty—the right to free speech—also encroaches on the right of doctors to practice medicine.

The notion that the government can censure our first liberty through the power of the federal purse strings—and that states can challenge the courts to overturn our fundamental rights—is repugnant and dangerous for all Americans. Women face the loss of the fundamental right to liberty in the controversy over control of our most private reproductive decisions. And, as has been the case in the past in this struggle, poor women suffer first and hardest.

Another aspect of the bigger picture is that the precious wall between religious dogma and government policy has been rent. In 1989, in *Webster v. Reproductive Health Services,* the Supreme Court let stand the preamble to a Missouri anti-abortion law which says, "The life of each human being begins at conception." In his dissent, Justice Stevens said the preamble is "an unequivocal endorsement of a religious tenet" that "serves no identifiable secular purpose."

This ever-expanding web of repression encompasses the Bush administration's view that it is appropriate for others to interfere in a woman's right to freely travel. The Justice Department joined with Operation Rescue in arguing before the Supreme Court, in *Bray v. Alexandria Wom-*

Adapted from the author's Commencement Address to the Class of 1992 of the Mount Sinai School of Medicine on May 11, 1992. At the time of this address the author was immediate past president of Planned Parenthood Federation of America; she is now developing a nationally syndicated television show on women's and men's issues.

en's Health Clinic, that a federal statute passed in 1871 to protect blacks from the mob violence of Ku Klux Klan does not protect women travelling to abortion clinics from the mob violence of Operation Rescue. It is an outrage that this administration gives aid and comfort to violent mobs that use the weapon of intimidation against women and doctors. Our right to travel freely is fundamental to our way of life as Americans.

As you have prepared yourselves to serve humanity, you must not lose sight of the threats to your right to provide those services and the right of your patients to receive those services.

Each of you has an obligation to actively work to change the nature of this debate—to actively counter the extremists' attempts to cast women as unconcerned about the consequences of our sexual decisions.

You can help foster an understanding of the true nature of America's problems with sexuality and reproduction—the fact that

- half of the six million pregnancies in this country every year are unintended
- America has the highest rates of teenage pregnancy, childbearing, and abortion in most of the developed world
- 100,000 women in this country have HIV, and women are the fastest-growing group of people with AIDS
- 3,000 children in this country have already been born with AIDS.

And to counter the extremists' focus on punishment and oppression, you can be leaders in challenging the fears about our sexuality, and our greater comfort with mandating AIDS education than with mandating sexuality education.

This is the bigger picture that must shape your resolve and your work. You enter a profession under attack and in turbulence over these other issues that are fundamental to the practice of medicine. Those who are most threatened, the poor and the young, will depend on your position of privilege and influence to articulate their needs and defend their rights.

You have accepted a calling to serve people without requiring them to be accountable to your personal moral standard. If you are to meet that challenge, the political dimension of your profession must be a part of your work. To ignore that political dimension—on which you can have a great impact—is to imperil the health of your patients, and to render your efforts ineffective against the forces determined to punish the poor and to reverse the progress of women.

Political power is never bestowed. It must be seized—often as the result of a seminal event, such as the Clarence Thomas hearings. Government is not an abstract concept. We, the people, must control what our government does.

Let our efforts be guided by the words of Judge Learned Hand: "Liberty lies in the hearts and minds of men and women. When it dies there, no Constitution, no law, no court can save it." Let us heed those words. Let us accept the burden—and the honor—of keeping liberty alive in our hearts, so that we may preserve and protect the health and well-being of all future generations.

Science, Scientists, and Responsibility

Kenneth I. Shine, M.D.

NOT LONG AGO, I presented the case of an interesting patient to a group of medical students. He is a 54-year-old man who had participated in clinical trials of genetically engineered erythropoietin. The drug changed his life. For the previous 14 years, the patient had been on chronic kidney dialysis. Although the treatment had adjusted many of his metabolic parameters, he continued to be weak, anorectic, and anemic. He could not work, was sexually impotent, and could not play with his grandchildren for more than a few minutes. Erythropoietin not only largely corrected his anemia, but treatment was associated with a dramatic change in his appetite. Indeed, he required careful counseling in order that the food he craved not provide more potassium than his routine dialysis had handled. His strength improved remarkably so that he could return to work, resume sexual activity, and play with his grandchildren without limit. For him the availability of this drug was a medical miracle and a triumph of biomedical science.

Modern Medicine in Microcosm

Several features of this experience deserve our careful consideration. In the 1950s important experiments had been done in dog models of anemia which demonstrated that plasma from an anemic dog could raise the blood count in other animals. These physiologic experiments, performed in an animal model, ultimately led to the isolation and purification of the active agent. During the period in which these experiments were underway, I had the opportunity as a college undergraduate to take a seminar from a tall, gangling American who had returned from England a short time earlier, where, with Francis Crick, he had described the double helix. In a seminar conducted by James Watson, we speculated about how long it would take to break the genetic code and allow the production of important proteins in vitro. Many of us were convinced that by the end of the century, the code would be understood and proteins could be produced. As with so many predictions, we knew the direction, but had absolutely no sense of velocity.

The development of erythropoietin for clinical use dramatizes the remarkable way in which various elements of science connect to produce a clinically useful result. From animal physiology to molecular biology to pharmacology, various disciplines of science came together. From the laboratory to the bedside, the distance has been shortened both in space and time. As a consequence the products of most fundamental science reach the patient in extraordinarily short periods of time. The identification by Slamon and colleagues of oncogenes critically related to the natural history of breast cancer was followed by clinical trials of the protein product within 18 months.

The case dramatizes other aspects of modern science. The company that now manufactures erythropoietin was established in collaboration with university faculty. The early clinical trials of which this patient was part were carried out by that company in collaboration with university faculty, including some at the University of California at Los Angeles. By 1988, the investment by industry in biomedical research had exceeded that of the public sector. With increasing constraints on federal support of biomedical research, in the face of a huge budget deficit, it is likely that the industrial research component will grow at a substantially more rapid rate than that of academic centers. Moreover, many critical

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pieces of equipment, technology, reagents, and drugs will be in control of industry but will be essential to the activities of academic scientists. Since conflict of interest is an important issue of accountability for contemporary science, and members of the UCLA faculty participated in clinical trials, I have avoided any personal, financial, or other interest in the company that developed erythropoietin. Erythropoietin is only one of many important therapies developed out of an industrial-academic collaboration.

The patient's experience also identifies some critically important issues in health care delivery. Last year Medicare spent over $4.4 billion on long-term kidney dialysis provided to some 58,000 patients throughout the United States. Treatment of these patients was so profitable that a variety of free-standing, for-profit enterprises arose to treat such patients. Erythropoietin and the drug itself is so expensive that some components of the health-care system, for example the Veterans Agency hospitals, have had a limited capacity to provide the drug to their patients. Yesterday's newspapers described the lower utilization of this drug by black patients than by white patients, a use pattern thought to be partially the result of the large patient copayment required.

In a recent analysis of health-care costs in the United States and other industrial nations, Joseph Newhouse has concluded that the largest single factor contributing to the high rate of increase of health-care costs in the industrialized nations has been the diffusion of technology, accounting for approximately 50% of the rate of increase. He and others have pointed out that the capacity to recapture the investment in technology not only in the United States, but also for companies in Europe and Japan, has been largely based on the ability to reap substantial product profits in the American health-care market, and that control of health-care expenditures in the United States would have an impact on technology development in companies throughout the world.

In a microcosm, then, this patient's case demonstrates some of the extraordinary features of modern medical science. Never have the opportunities been greater for discovery and innovation. The pace of science continues to accelerate, not only in terms of new discovery, but in communications between scientists throughout the world and the capacity of science to take place in other countries—in industry as well as in the American university. Results of these discoveries have been expensive. Developments in industry and the federal budget could limit the capacity of basic science conducted within the university to maintain America's preeminence in this area.

The American research university is one of the last remaining areas of this country's international leadership. But it is threatened. Not only is direct research support under pressure; the high cost of tuition and student debt is an increasing problem. Increasing efforts to control health-care expenditures limit the extent to which medical schools can seek support from patient-care income. The recent emphasis on universities sharing the cost of research has arisen out of the budget deficient and the furor over indirect cost reimbursements. Confidence has also been undermined by revelations of scientific misconduct, which is uncommon but has been poorly handled by the scientific community.

Greater Accountability and A Larger Social Ethic

All these developments demand a higher degree of accountability by scientists and physicians, accountability for science and for its scientific products. As is well demonstrated by the erythropoietin story, there is no area of science so basic that it cannot have a direct, rapid, and in some cases expensive impact on the society in which scientists work. As scientists and physicians we must be accountable for our conduct and that of our peers. The recent David report of the National Academy of Sciences was notable not only because of its definition of scientific misconduct, but for the clear statement that scientific misconduct is real, which is still denied by some, that it must be recognized, and that it must be dealt with effectively and expeditiously. In my judgment the manner in which some elements of the scientific community responded to scientific misconduct and the initial response by some to the issues of indirect cost recovery within research universities undermined the credibility and the sense of accountability of the scientific community, which is crucial if scarce resources are to be provided for science. Too often the arguments for increasing the scientific budget have been based on the concept that science is valuable and must be supported in its own right. Yet scientific research is competing with education, social services, and a variety of other socially desirable activities.

Scientists must clearly identify the importance of what they do in relation to improvements in health and biotechnology. When new technologies are developed, both scientists and physicians must ask hard questions about whether the new development is in fact a significant advance over what was previously available and will replace preexisting technology, or whether it is simply going to be marginally additive. In this regard, research in health services, with an emphasis on outcomes and effectiveness of care, will be a critical component of any reform of the health-care system and in understanding the value of new science and technology. Medical schools must support faculty who can bring knowledgeable skills to bear on this issue in every discipline of medicine.

Accountability also is crucial as we undertake reform of our health-care system; hard questions about what is to be done must be asked. We are increasingly aware of the role of ethics in informing individual decisions made by individual physicians, patients, and families in the course of health care. We are also aware of the concept of professional ethics as it relates to the role of medicine and science. But there is a need for a larger social ethic that addresses the question of what is right and proper in the way society uses its resources and sets its priorities. The advances in dealing with chronic kidney disease are remarkable and often extremely useful. But how do we balance $4.4 billion for long-term kidney dialysis with circumstances in which two out of three preschool Hispanic children in Los Angeles County are not immunized, or with the fact that modest investments in prenatal care would produce not only healthier babies, but ultimately decrease the cost of neonatal intensive care? As scientists and physicians, we must be concerned not only about the development of new knowledge; we also have a responsibility for how that knowledge is used and to whom it is made available.

Finally, scientists have been concerned about identifying young investigators. There is an increasing awareness of the importance of increasing the size of the pool of scientists from minority backgrounds as well as enhancing the role of women in science. From time to time scientists raise concerns about the pipeline for future scientists. We know that it depends critically on science education in the K–12 segment of our educational system. Led by Bruce Alberts and others, scientists have made an effort to reach out and enhance math and science education in the public schools. A number of medical schools around the country have had excellent initial experiences, and one or two have had long-term experience with math and science education in the public schools. This is an area in which academic health centers can show their accountability for both education and science in a dramatic way. There are a variety of models available in which the faculties and the students in American academic health centers have created programs in collaboration with teachers of math and science and, in some cases, with public-school students themselves. Academic health centers could provide no greater community service than to form alliances in which the considerable energy of faculty and students could be used to stimulate and to educate underrepresented students in the public schools.

Despite all the challenges we face in academic health centers, we are a privileged community, well educated and well compensated. Recognizing and acting on the need for accountability is ethically and socially essential. In so doing we increase society's confidence in us and in what we do, and the long-term result can only be beneficial for everyone involved.

Jamel L. Oeser, a 16-year-old student at Dr. Martin Luther King High School in New York City, is enrolled in the Secondary Education Through Health Program (SETH), and is undertaking his research apprenticeship in the Mount Sinai Clinical Microbiology Laboratories, working directly with Dr. Edward J. Bottone. Jamel is studying the role of the loofah sponge as a potential public health problem in the transmission of bacteria to the human skin. Jamel's work has been recognized by the National Institutes of Health, and he is also active in numerous community service projects. He has been writing poetry for about 10 years, mostly while traveling to and from school on the New York subways.

Heroism

Where black heritage flows from within,
And to be somewhat lighter is as bad as sin.
Take a look at my life.

In my mind I see forests where brown chipmunks dash,
But through my eyes all I see are rats in the trash.
Take a look at my life.

The bullets are flying. Drugs are easy to sell.
If this is Heaven, I'd hate to see Hell.
Take a look at my life.

Where poverty and hunger are seen as disease,
And all that's ever heard from a policeman is the cold word freeze.
Take a look at my life.

Where green trees, grass, and mountain tops
Are replaced by abandoned buildings, crack bottles, and slop.
Take a look at my life.

Where dreams are lost and good things die,
And there's no such thing as apple pie.
Take a look at my life.

Where a young black man has been robbed of his life,
And the media would rather cover a man's affair with his wife.
Take a look at my life.

Where the number of unemployed skis down the slope,
And a young teenage mother can no longer cope.
Take a look at my life.

Where a high-school graduate feels like a fool,
He was a first-rate student in a third-rate school.
Take a look at my life.

An old woman walks by and she clenches her purse.
When asked my opinion, I'm expected to curse.
Take a look at my life.

Where me and my friends are supposed to be thugs,
And I see a good friend losing the battle with drugs.
Take a look at my life.

Where a person educated is labeled a geek,
By "friends" he's tormented because he knows how to speak.
Take a look at my life.

Where as one teacher put it, slavery's not dead,
The shackles have moved from the wrists to the head.
Take a look at my life.

Where babies are common but fathers are rare.
They'll all grow up bastards—now how is that fair?
Take a look at my life.

A girl plays in the park, fun and laughter's the sound.
Just then she is shot, her head hits the ground.
Her mother encloses her body, hate sharp as a knife.
Her tears bathe her girl's body as it starts to lose life.
Take a look at my life.

Where a man examines his life and lets out a sigh.
He knows there is one way out—that escape is to die.
Take a look at my life.

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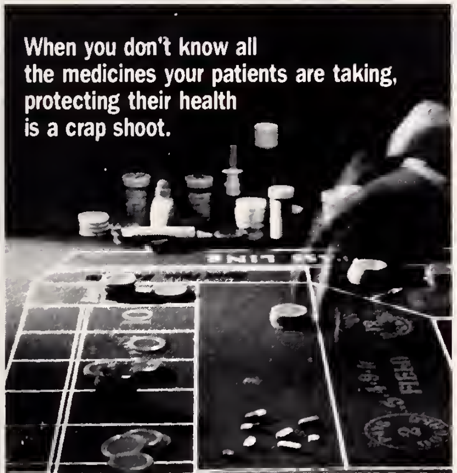

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Osteoporosis:

On the Verge of Rational Effective Therapy?

JOHN P. BILEZIKIAN, M.D.

I HAVE SUBTITLED this presentation "On the Verge of Rational, Effective Therapy" because I think we probably are at that verge for osteoporosis, one of the most important chronic disorders of life. When I was just beginning to work in this field, twenty years ago, one of my mentors said to me, "There hasn't been a good idea in osteoporosis in the past 300 years." But over the past twenty years, the field has changed rapidly; we know much more about calcium metabolism than we did, and this knowledge has led to new ideas with respect to pathophysiology and therapy of osteoporosis (1). After a brief introduction to calcium metabolism, I will concentrate on proposed therapeutic regimens for osteoporosis, an area about which new information is rapidly becoming available.

Calcium Metabolism

Three organs, the skeleton, the gastrointestinal tract, and the kidney, interact with a set of calcium-regulating hormones to keep the human skeleton sound and the circulating calcium level within normal limits. An active process involving the gastrointestinal tract, mediated in part by vitamin D, permits absorption of a certain amount of calcium. The kidney, under the influence of parathyroid hormone and phosphate, regulates the amount of 1,25-dihydroxyvitamin D available to enhance calcium absorption. The skeleton, under the influence of both parathyroid hormone and 1,25-dihydroxyvitamin D, undergoes constant remodeling. Daily, a substantial amount of calcium is accreted into bone and resorbed from bone.

The cells important in the remodeling process in bone are osteoblasts and osteoclasts. Osteoblasts are responsible for forming the organic matrix of bone, the osteoid. The mineral phase of bone, calcium hydroxyapatite, is deposited onto the osteoid in a manner and under circumstances that are highly ordered but poorly understood. Osteoclasts, multinucleated giant cells, are responsible for resorption of bone, a process that actually initiates the bone remodeling sequence. Bone remodeling, the process by which bone is normally turned over every day, begins with the osteoclast literally taking a bite out of bone, thereby excavating a cavity. The results of osteoclast activity are associated with an intercellular signalling event, leading to recruitment of osteoblasts, which begin to fill this cavity with new organic matrix. The organic matrix is then mineralized. If everything is in balance, the quantity of bone removed is matched by the quantity of bone formed. There is neither gain nor loss of bone. The dynamic steady state turns over regularly approximately 500 mg of calcium, as much calcium as is found in two 8-oz containers of milk.

This homeostatic mechanism begins to break down in all adults such that more calcium is lost from the skeleton than is gained. The slight imbalance, which is believed to begin in the mid-30s, is virtually imperceptible and certainly not appreciated by routine studies. However, over the decades, extremely minor daily calcium losses may become clinically evident in reduced bone

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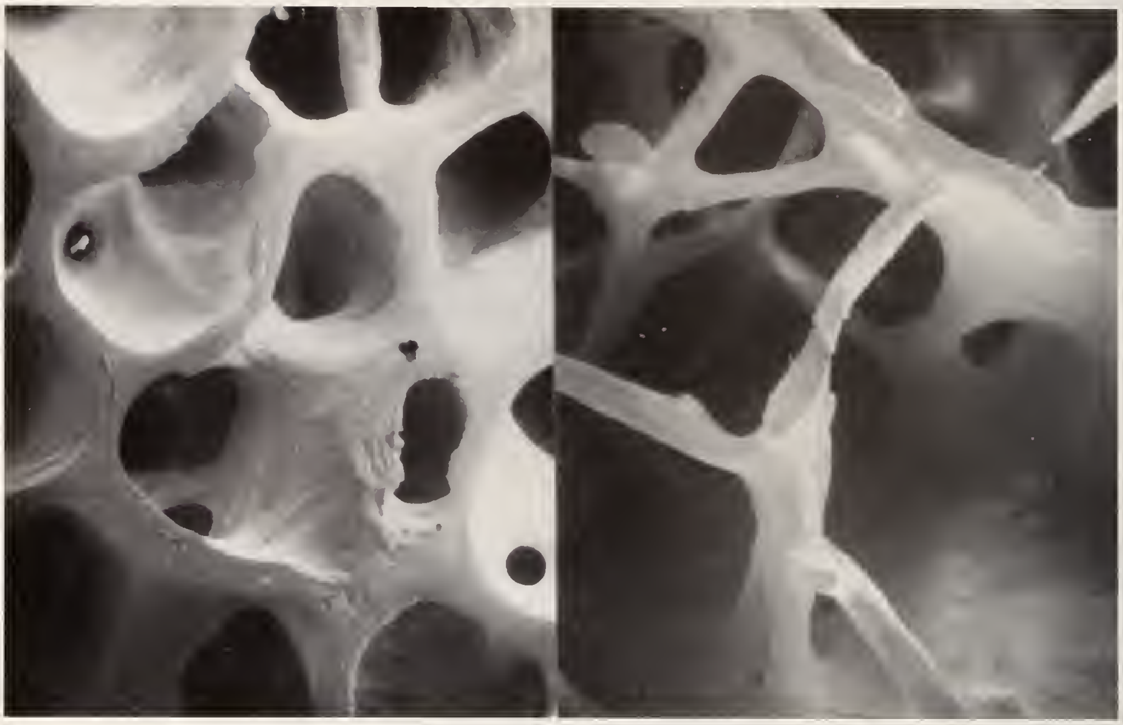

Fig. 1. Osteoporosis as seen by scanning electron microscopy. Low-power scanning electron micrographs of iliac crest biopsies from normal **(left)** and osteoporotic **(right)** bone. Note reduction in trabecular plates and their discontinuity in the osteoporotic specimen as compared to normal biopsy. *Adapted* from Dempster DW, Shane E, Horbert W, Lindsay R. A simple method for correlative light and scanning electron microscopy of human iliac crest bone biopsies. J Bone Min Res 1986; 1:15–21.

mineral density, eventuating in the syndrome osteoporosis. As one loses more and more bone, one is more and more subject to the possibility of fracture at those sites of reduced bone mineral density. Individuals who have lost bone beyond a certain amount—the so-called fracture threshold—are at definite risk for skeletal fracture. The presence of reduced bone mineral density, however, does not predict fracture in any one individual. An intervening event, most likely a fall or other form of mechanical stress, is required for the fracture to occur.

In the vertebral spine, the crush fracture of one vertebra may become associated with other vertebral crush fractures, leading to the clinical appearance of osteoporosis. Loss of height and a kyphotic configuration of the back gives a picture all too commonly seen in postmenopausal women in this country. Men are not spared this disorder of the aging skeleton. It begins to become evident in men approximately a decade later than in women. We are all likely to develop significant risk for osteoporotic fracture if we live long enough.

TABLE 1
Risk Factors Associated with Osteoporosis

Definite risk	Probable risk
Female sex	Sedentary life style
White or Asian origin	Nulliparity
Positive family history	Extreme thinness
Early menopause (or oophorectomy)	High caffeine intake
Cigarette smoking	High protein intake
Alcohol abuse	
Lifelong low dietary calcium intake	

Osteoporosis is a problem not just in the way people look, or a problem in back pain, which can be a source of great morbidity; it is also an enormous economic problem. Osteoporosis is an economic problem because of its association with hip fracture, an event in older women often accompanied by substantial morbidity and mortality. The osteoporotic hip fracture, a most common cause for hospitalization in octogenarians, generates a huge medical bill for this country. Literally, billions of dollars are spent on health care issues related to the fractured hip.

Fuller Albright, the father of this field, defined osteoporosis over 50 years ago as "too little bone," tellingly depicted in **Fig. 1.** Osteoporosis is also an architectural problem. Normal bone has an interconnected honeycombing network that helps to provide structural integrity. In osteoporosis, there is not only a reduction in bone per

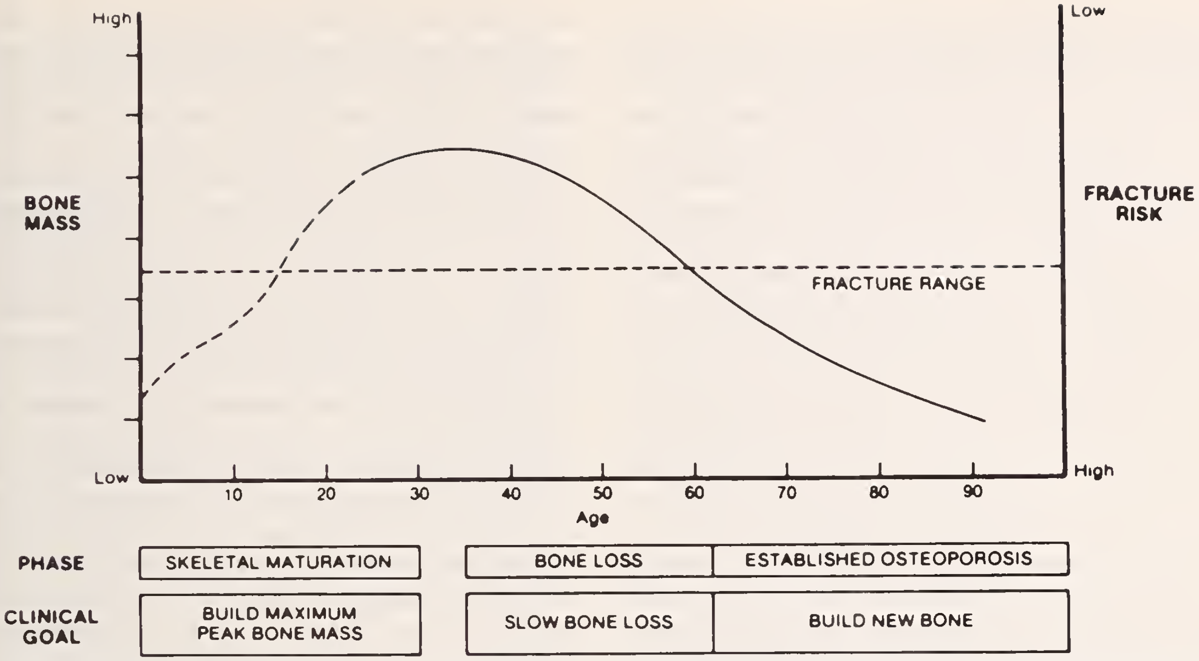

Fig. 2. Gain and loss of bone mineral as a function of age. This schematic depiction of skeletal maturation, stability, and loss is shown in relationship to fracture risk and clinical goals. *Adapted* from Wasnich RD, Ross PD, Davis JW. Osteoporosis: current practice and future perspectives. Trends Endocrinol Metab 1991; 2:59–62.

unit volume but also a loss of connectivity. As shown in the figure, some trabecular plates are completely lost, while others are in the process of losing their base of support (2). It is this problem, loss of structural integrity, in addition to loss of bone mineral, that is the challenge in the therapy of osteoporosis. Somehow, connectivity of trabecular plates must be restored if mechanical strength is to be regained. Successful therapy, thus, is not simply a matter of stimulating skeletal calcium accretion but a problem in rebuilding normal skeletal architecture.

Risk Factors. Some risk factors for osteoporosis (Table) are well-defined, as for example being female. White and Asian populations are also clearly at greater risk than black populations, which appear to be relatively well-protected. A positive family history is considered to be an important risk factor. An early menopause, whether spontaneous or surgical, clearly places an individual at greater risk for developing osteoporosis. Alcohol abuse is now widely acknowledged to be a significant risk factor, especially among men. Cigarette smoking also appears to be detrimental to the skeleton. Other potential factors such as lack of exercise, poor calcium diet, caffeine intake, and phosphate intake are all under active investigation.

Achievement of Peak Bone Mass. Does the problem of osteoporosis begin in childhood and adolescence? Bone mass is increasing from childhood through the early to mid 30s, and then inevitably and inexorably declines. The decline in bone mass is an age-dependent phenomenon, and occurs without regard to the presence or absence of risk factors. Achievement of peak bone mass, or lack thereof, may well be a major point separating those who become clinically osteoporotic from those who do not. Achievement of peak bone mass may well be related to events in one's life when bone mass is increasing, that is, in the earlier years before full adulthood is reached. A few areas of potential relevance in this regard include dietary intake of calcium as well as other nutritional factors; activity level; weight; menstrual history; genetic factors (3–5). One must distinguish this osteoporosis due to age-related bone loss (type II osteoporosis) from loss of bone mass due to estrogen deficiency, so-called postmenopausal osteoporosis (type I osteoporosis). It is important to recognize that the effects of estrogen loss are superimposed on age-related bone loss.

Differential Diagnosis of Osteoporosis. The differential diagnosis of osteoporosis is not simply a matter of determining whether bone loss is a phenomenon related to age (made worse by the presence of risk factors) or to menopause. Osteoporosis can be due to a host of endocrine diseases, such as Cushing's syndrome, hypogonadism, hyperthyroidism, or severe primary hyperparathyroidism. Corticosteroid-induced osteoporosis is probably the most common secondary type of osteoporosis. Malignant conditions such as multiple myeloma and metastatic cancer are well-recognized causes of skeletal demineralization. Immobilization can lead to demineralization. It is a matter of good medical practice to consider other causes of osteoporosis, especially in patients for whom the presentation or severity of the condition is unusual.

Bone Densitometry. Measurement of bone mineral density has become an integral part of the diagnostic evaluation of a patient who is suspected to have osteoporosis. A matter of controversy is the site to monitor. The three major sites of clinical concern are the vertebral spine, the hip, and the distal forearm. Although there is a literature that argues that certain sites in the skeleton (the ultradistal radius and the calcaneous) are representative of the skeleton in general, these observations are most likely to be valid only when large population studies are performed. For a given individual, a particular site might not be representative of other sites and, in fact, may be misleading. This point is not surprising considering the fact that the three major sites are comprised of different proportions of cancellous and cortical bone. Even sites such as the ultradistal radius and the calcaneous, which are enriched in cancellous bone, may not be accurate markers of the cancellous bone in the vertebral spine. It is now generally agreed that direct measurement of the skeletal site(s) of concern is the best way to obtain the most accurate information.

A new technology of bone mass measurement, quantitative digital radiography, also referred to as dual energy x ray absorptiometry, is rapidly replacing methods such as single and dual photon absorptiometry (6). This technology is extremely precise (on the order of 1%) and accurate (on the order of 3%–5%). Such densitometers can be used not only for ascertaining bone mineral density at selected sites but also to monitor change over time with or without therapy.

Therapy of Osteoporosis

Therapy of osteoporosis has three different aspects that can be formulated as questions:

- How do we achieve peak bone mass?
- How can we reduce the magnitude of calcium that is eventually lost from bone?
- Among those who have sustained bone loss, how can we restore bone mass in such a way that the skeleton also regains its structural integrity?

Fig. 2 illustrates these aspects as a function of a life timeline. To meet these three therapeutic aims, the list of potential approaches is long. Some approaches are applicable to more than one of these aims. I will discuss the following three general categories: calcium and exercise; hormonal agents; pharmacologic agents.

Calcium. "Sticks and stones will break my bones, and so will too little calcium." Many people think this cute comment may also be telling insofar as the nutritional value of calcium to the skeleton is concerned. Put another way, the composition of your bones may reflect what you eat. The well-known Matkovic study compared two populations that were well-matched except for their lifelong history of dietary calcium. Subjects whose diet had been high in calcium had an incidence rate of hip fracture markedly lower than those whose diet had been low in calcium (3). Although studies like this one are few and far between, they do support the notion that calcium intake in childhood and early adolescence is instrumental in helping to achieve peak bone mass.

Whether calcium intake is a critical factor after the skeleton has completely matured is even more controversial. A recent study published in the New England Journal of Medicine (7) showed that among subjects whose intake was less than 400 mg of calcium, which is indeed a low-calcium diet, supplemental calcium helped with respect to spine, femoral neck, and radius bone density, but individuals whose intake was between 400 and 640 mg did not appear to benefit from supplemental calcium. This study illustrates that in older postmenopausal women, a diet obviously deficient in calcium probably is detrimental to maintaining bone mass.

What is the recommended calcium intake in this country? The Food and Drug Administration has raised the recommended daily requirement to 800 mg in the premenopausal state. Most investigators in the field believe it to be closer to 1,000 mg, the amount of calcium contained in about a quart of milk. In postmenopausal years, the calcium requirement may increase to 1500 mg. Where do we get our dietary calcium from? We get it best from dairy products. Milk, for example, is an excellent source of calcium. Of course, other dairy products can also serve as excellent sources of dietary calcium. With respect to green vegetables, kale and broccoli contain bioavailable calcium, which is not as true for spinach.

It is difficult to obtain 800 to 1000 mg of calcium through food alone. This is due, in part, to concerns about calories and cholesterol, which has limited the intake of dairy products in many individuals. Parenthetically, low-fat and skimmilk products contain as much, if not more, calcium than high-fat dairy products. However, even persons who have a reasonably normal diet are unlikely to take in 800 mg. Thus, calcium supplements are usually necessary. There are many forms of calcium available: calcium carbonate, calcium citrate, calcium gluconate, calcium lactate, calcium glubionate (8). The particular form of calcium does not really matter, but calcium carbonate provides more calcium per weight of compound than do the other calcium salts because the carbonate ion is relatively small compared to the other ions. In terms of cost, some of these calcium preparations, when sold as brand names, are quite expensive. Generic calcium carbonate can be very inexpensive. The objective of calcium supplementation is to reach a total (diet plus supplement) of 800–1000 mg in the premenopausal years and about 1500 mg in the postmenopausal years.

Are kidney stones a potential problem with calcium supplementation? Actually, unless there is a history of calcium stones, one does not have to be concerned because it is rare, if not unheard of, for this to be a complication of supplemental calcium administration.

Exercise. Exercise is an important therapeutic strategy in osteoporosis (9–19). A study from Australia by Pocock, Eisman, and their associates indicated that cardiovascular conditioning associated with exercise, as measured by VO_{2max}, was actually related to bone density of the femoral neck (11). Thus, conditioning alone could improve bone mineral density. Questions have been raised about whether exercise per se is important or whether in fact the exercise has to be targeted with respect to general antigravity stress. Antigravity exercises such as walking and running are, in this respect, considered to be beneficial. Recent attention has been paid to sites of mechanical stress caused by certain exercises. Tennis players who stress their dominant arm by serving have greater bone density of that serving arm than the other one. Exactly how exercise improves bone mineral density is controversial. There is no question, however, that exercise is good and is generally to be recommended. It is to be recommended at all ages and even, with some qualification, to those with established osteoporosis.

Exercise is not always beneficial. Certainly in osteoporotic women who have already sustained compression fractures or in those who have markedly reduced mineral density, exercise can be detrimental. If not advised properly on exercise, patients can subject themselves to adverse musculoskeletal stresses. Another example of the detrimental effects of exercise is in the premenopausal woman who becomes oligomenorrheic or amenorrheic due to excessive exercise. These women are at risk for an estrogen-deficiency type of bone loss. In a study by Marcus et al., exercising women with regular periods were compared to exercising women with amenorrhea (12). There was a marked reduction in bone mineral density of the spine in the amenorrheic women. Thus, exercise must be undertaken in moderation and with due regard to the importance of maintaining regular cycles. For most normal purposes, exercise is not going to interfere with menstrual function unless it is extremely strenuous or associated with major weight loss.

Estrogen Therapy. The goal of estrogen therapy is to prevent bone loss. Estrogens do prevent bone loss. The minimal effective dose is 0.625 mg conjugated estrogen. Estrogens appear to be effective over the 5–10 year period beyond the menopause. If estrogen therapy is discontinued during this period, studies have shown that a period of relatively rapid bone loss may occur, similar to the loss that is typically experienced in women who enter the menopause without receiving estrogen therapy. Early data suggest that estrogens may even show some effectiveness well beyond the menopause (13).

Estrogens are used in a cyclical manner with a progestational agent. There are contraindications to the use of estrogens, such as a personal history of uterine cancer or thromboembolic disease. A family or personal history of breast cancer may be another cautionary note, but the data here are still very controversial. Unfortunately, many potential estrogen users and their doctors are generally reluctant to embark on an indefinite period of postmenopausal estrogen therapy and, thus, it is probably not used as widely as it should be.

Calcitonin. Calcitonin is an osteoclast inhibitor that may be effective in a form of osteoporosis characterized by high turnover where there is active bone resorption and bone formation ongoing (14). In these individuals, calcitonin seems to be effective. Whether calcitonin is effective in the more common presentation of postmenopausal osteoporosis, in which bone turnover is very inactive, is not clear.

Fluoride. Fluoride stimulates osteoblasts, the cell in bone responsible for bone formation. In many nonblinded studies that have investigated the use of fluoride in osteoporosis, the results have seemed to suggest that fluoride is really quite effective. However, recent well-designed studies have dampened enthusiasm for fluoride in postmenopausal women with osteoporosis (15). Using an average of 70–75 mg of fluoride daily, there was a spectacular increase in vertebral bone mineral density, up to 35% over a four-year period. The incremental effect was less dramatic for femoral sites and not seen at all at the radius.

One question that was critically important to answer in the study was whether the dramatic increase in bone mass was associated with a reduction in fracture incidence. This is an extremely important endpoint because an increase in bone mass does not necessarily mean an increase in structural integrity of bone. The study showed unequivocally that fracture incidence was not reduced when fluoride-treated subjects were compared with placebo-treated subjects.

The other significant outcome of these studies is the fact that the fluoride group experienced several adverse side effects, the most noteworthy ones being dyspepsia, gastrointestinal tract bleeding, and a lower-extremity pain syndrome. One can criticize these studies for using a relatively high dose of a short-acting fluoride preparation and for being relatively short term. But it is hard not to conclude that fluoride presents real problems as a therapy for osteoporosis. Any therapy for osteoporosis needs to be associated not only with improvement in bone mineral density but also with improved bone strength.

Bisphosphonates. Let us return to our model of bone remodeling in order to consider a strategy to overcompensate for the initiation of this process by osteoclasts. If osteoclasts are activated only partially, the excavation cavity will be less deep. The osteoblast then would fill in this more shallow cavity with a preprogrammed packet of bone matrix leading to a net accumulation of bone. I have described simply the essence of protocols based on the ADFR concept (*A*ctivation, *D*epression, *F*ree period, *R*epeat). These regimens have been popularized as “coherence therapy.” Two recent studies have compared bisphosphonate therapy with placebo for women with osteoporosis (16–17). The regimen consisted of two weeks of etidronate therapy and approximately 13 weeks of supplemental calcium. Etidronate was repeated with this same time frame over several years. In contrast to the recent fluoride studies, patients treated with etidronate showed a reduction in fracture incidence to accompany a modest increase in bone mineral density. The reduction in fracture incidence was actually greater among those with the lowest bone mineral density. Although these reports of bisphosphonate therapy for osteoporosis are encouraging, it is too early to know whether they will be upheld over a longer period of time. One would like to see a sustained, if not further increase in bone mass, along with continued reduction in fracture incidence.

Vitamin D. A brief comment on vitamin D therapy in osteoporosis: There is evidence that older subjects are deficient in their ability to produce 1,25-dihydroxyvitamin D due to an age-related decline in renal function. However, this deficit does not appear to be restricted to or worse in postmenopausal women with osteoporosis. Moreover, most older individuals in this country are not vitamin-D deficient. Nevertheless, some studies employing 1,25-dihydroxyvitamin D as a therapy for osteoporosis have shown beneficial effects (18). Others have not (19). There is a narrow therapeutic window for 1,25-dihydroxyvitamin D; hypercalcemia and hypercalciuria can occur depending on how much 1,25-dihydroxyvitamin D is used in conjunction with supplemental calcium. The dose of 1,25-dihydroxyvitamin D and supplemental calcium, thus, has to be adjusted carefully to prevent these adverse effects.

Summary

I would like to leave you with the following recommendations. In postmenopausal women without osteoporosis, calcium intake should be 1.5 grams daily, which in almost all such women requires supplementation of the diet. These women do not need vitamin D unless it can be shown that there is a vitamin D deficiency state present. They should not smoke and they should not drink alcohol to excess. They should exercise in a manner appropriate to their general physical condition. If they can take estrogens, they should take estrogens.

In women with established osteoporosis, many of the same suggestions are made with respect to calcium intake, vitamin D, tobacco, alcohol, and estrogens. In addition, if there is a high turnover state in bone—a situation that can be established only by bone biopsy—calcitonin may be efficacious. I think it is reasonable at this time to consider bisphosphonate therapy using regimens that have been published. This is advised, recognizing that the data are promising at this time only in the short term. Etidronate should not be considered for therapy continued beyond two years until more data are forthcoming.

The last thought I want to leave you with is that people are going to fall and sustain fractures. Accidents are going to happen. Even if we were to realize the most optimistic dream, to prevent osteoporosis in all people, fractures are still inevitable. However, when fractures do occur, one wants to have bones as intrinsically sound as they can possibly be. The goal, then, is to have a skeletal structure that is as healthy as possible, so that if a fracture were to be sustained, healing and recovery occurs under the most promising conditions.

Questions and Answers

Richard Gorlin: Thank you very much, John, for a spectacular overview. Let me ask you a question. Do you distinguish at all between the accumulation of calcium and the necessity to lay down a proteinaceous matrix first? Is there anything there that becomes important?

John Bilezikian: That's an important question. How the osteoid matrix is laid down is probably important because it is the substrate on which mineralization occurs. There are some examples of defects in osteoid formation, but those are usually congenital defects, associated with another kind of osteoporosis. In unusual and so far uncommon causes of osteoporosis in adults, there can be defects in osteoid formation.

Levitt: I enjoyed your talk enormously. I find intriguing this disparity between the improvement in bone density and the perseverance of fractures. Have data like that been accumulated for estrogen? Do you eliminate incidence of fractures with estrogen as well as increase the bone density?

Bilezikian: With estrogens, bone density is preserved but not increased. Fracture incidence is reduced with estrogens.

Question: Is there a place for bisphosphonate therapy in patients with multiple myeloma with extensive bone involvement?

Bilezikian: A good question. There are some data, not directly related to myeloma but to metastatic cancer in general. The data are still incomplete. A drug like a bisphosphonate might be appealing in the setting of a tumor that has a disposition to metastasize to bone. We need more information on this point.

P. Harpel: There's increasing use of estrogen patches in the treatment of postmenopausal women. Are there any data on whether that kind of treatment is effective in preventing osteoporosis?

Bilezikian: The estrogen patch is attractive for several reasons. The drug administered through the patch to the skin is estradiol, as compared to estrone, the principal ingredient in Premarin. Estrone must be converted in vivo to estradiol. The patch eliminates the need for this conversion step. For this and other reasons having to do with uptake of estrone in the liver, the patch obviates potential hepatic problems which occur sometimes with oral estrogens. Another point of note is that the dose of estradiol administered by the skin patch is absorbed much more evenly and slowly than is the oral drug. The problem with the skin patch is that so far the adhesive used is associated in a fair number of women with local skin reactions. With regard to the question of efficacy, early data do suggest that the skin patch is effective.

Stein: In your list of predisposing factors, you listed a high-protein diet. Are you surprised by that?

Bilezikian: A high-protein diet may be associated with calcium loss in the urine, but not enough is known about this point to strongly implicate a high-protein diet in bone loss.

Gorlin: Thank you very much, Dr. Bilezikian. We learned a lot.

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The Pathophysiology and Molecular Genetics of Beta Thalassemia

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THALASSEMIA is a hereditary disorder of hemoglobin synthesis (1, 2). Hemoglobin is a tetramer of two different globin chains: two α and two β ($\alpha_2\ \beta_2$). For normal red blood cell metabolism, it is important to have equal amounts of α and β chains, because any excess chains that accumulate in the cell are insoluble and precipitate, causing cellular damage.

Pathophysiology and Clinical Manifestations

Synthesis of the relative amounts of alpha and beta chains is measured by incubation of peripheral blood in the presence of a radioactive amino acid followed by separation of the globin chains by column chromatography and quantitation of the radioactivity incorporated into nascent globin chains. In normal individuals, there is equal synthesis of α and β chains (**Fig. 1**). The basic biochemical defect in thalassemia is an imbalance between α- and β-chain synthesis, which can easily be demonstrated by the technique of isotopic labeling. In patients with homozygous β thalassemia, only a small amount of radioactivity is incorporated into newly synthesized β chains, as compared to that incorporated into α chains (Fig. 1). This disorder, in which some synthesis of structurally normal β chains takes place, but in markedly reduced amounts, is referred to as β^+ thalassemia. In other patients with β thalassemia, there is a total absence of β-chain synthesis, and that condition is referred to as β^0 thalassemia.

Two phenomena result from this imbalance of globin chain synthesis. First, because of the quantitative deficit in beta-chain synthesis, there is reduction in the total amount of hemoglobin that can accumulate in the cell as $\alpha_2\ \beta_2$ tetramers. But secondly, a more important factor in the pathophysiology of the disorder is the fact that excess α chains are synthesized and accumulate in the cell. These excess α chains are the cause of most of the cellular damage and hematologic abnormalities. The peripheral blood smear from a patient with homozygous β thalassemia demonstrates two major characteristic findings. First, the red blood cells are quite hypochromic due to decreased hemoglobin content as a result of the deficient β-chain synthesis. But in addition, there is a great deal of variation in red-cell size and shape, with red-cell fragments and increased numbers of reticulocytes and nucleated red cells. So, in addition to hypochromia due to deficient hemoglobin synthesis, there is a hemolytic component. The accelerated destruction of β thalassemic red blood cells results from accumulation of excess α chains. Although one cannot see them in regular blood smears, the excess α chains are visible as inclusion bodies or Heinz bodies when the blood is examined by phase microscopy (**Fig. 2**) or by supravital staining.

These inclusion bodies damage the red cells in a number of ways. The solid nondeformable physical mass of the inclusion body impairs the ability of the red cells to navigate through the microcirculation, in particular the microcirculation of the spleen, where the red cell has to go through very narrow passages. Unable to go from the splenic pulp into the venous sinusoids, the thalassemic red cells become trapped and are de-

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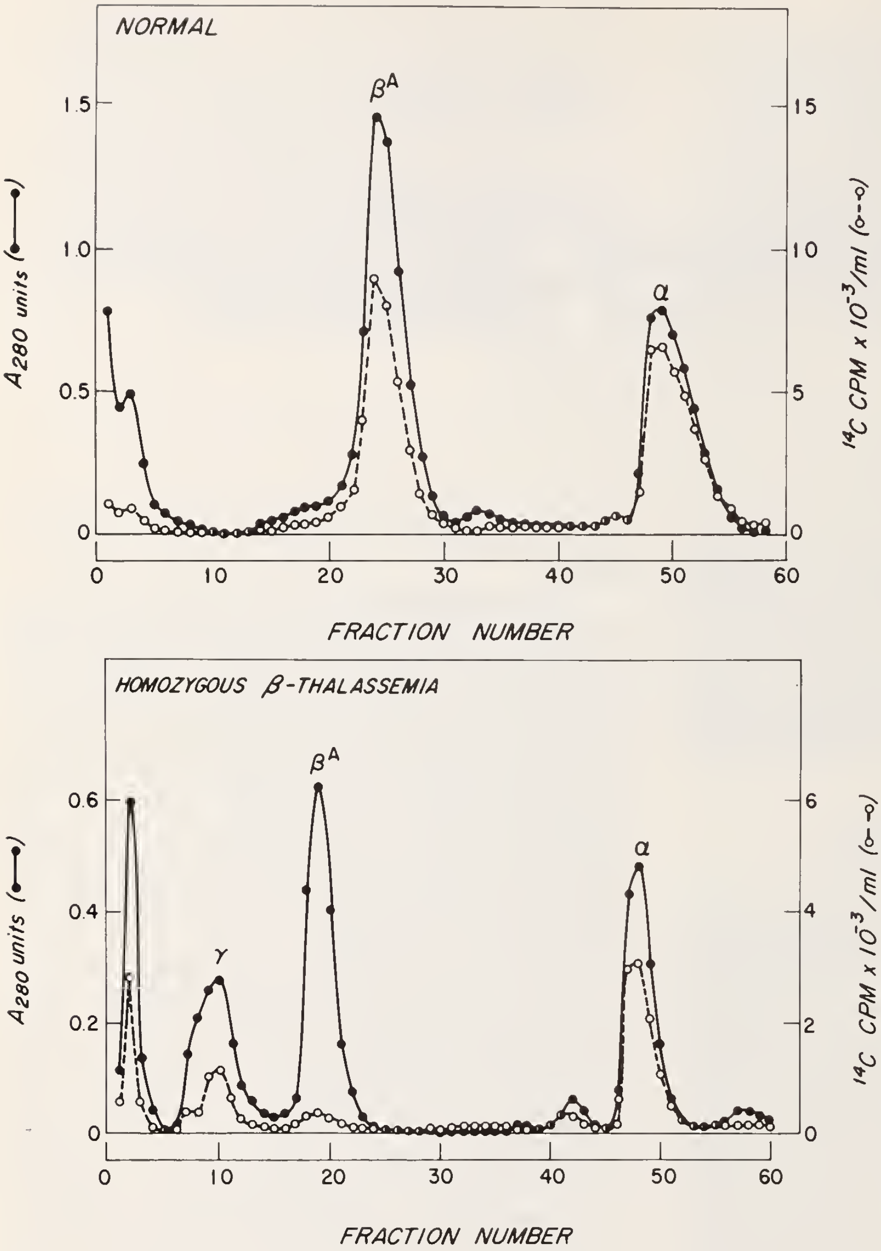

Fig. 1. Globin chain synthesis in human peripheral blood reticulocytes. After incubation in presence of a radioactive amino acid, globin was prepared from red cells and fractioned by carboxymethylcellulose column chromatography. ●--● represents optical density of globin chains; ○--○ represents radioactivity incorporated into newly synthesized globin chains. **Top** Nonthalassemic individual; **bottom** Patient with homozygous β$^+$ thalassemia. *Reprinted* with permission from Forget BG, Kan YW. Thalassemia and the genetics of hemoglobin. In: Nathan DG, Oski FA, eds. Hematology of infancy and childhood. Philadelphia: WB Saunders, 1974, 450–490.

stroyed in the spleen. In addition, the precipitated α-globin chains damage the red-cell membrane, either directly or as a consequence of removal or "pitting" of the inclusion bodies from erythrocytes by reticuloendothelial cells (Fig. 2).

The process of inclusion-body formation occurs not only in the mature circulating red cells, but also in the developing nucleated erythroid precursor cells in the marrow. There is a tremendous amount of destruction of these precursor cells in the marrow as a result of the membrane damage caused by inclusion body formation. The vast majority of cells are destroyed in situ in the marrow, only a small proportion of cells becoming circulating erythrocytes. This process is called ineffective erythropoiesis.

As a result of the ineffective erythropoiesis, erythropoietin production is stimulated, and tremendous proliferation of the erythroid marrow in all of the bones of the body takes place. The skull X-ray of a patient with homozygous β thalassemia shows the typical "hair-on-end" appearance due to thickening of the outer table of the skull, as well as expansion of the frontal and maxillary bones. The typical mongoloid facies of patients with homozygous beta thalassemia is the result of pronounced erythroid marrow proliferation in the bones of the skull.

The once typical thalassemic facial deformity is in fact preventable and is no longer seen in younger patients because of current improved treatment. With proper transfusion therapy, one

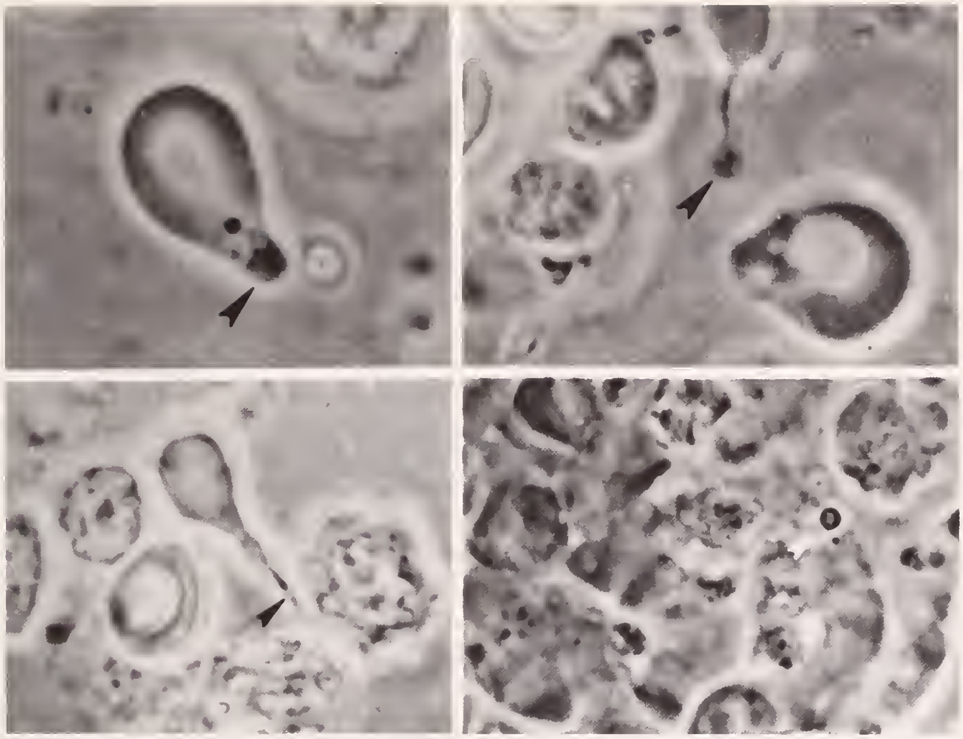

Fig. 2. Phase microscopy of cells from spleen of a patient with homozygous β thalassemia. Inclusion bodies consisting of precipitated α-globin chains (arrows) appear to be removed or "pitted" from a red cell by splenic reticuloendothelial cells (lower left) and are found free in the splenic pulp (white arrow, lower right). *Reprinted* with permission from Nathan DG. Thalassemia. N Engl J Med 1972; 286:586–594.

can prevent the erythroid hyperplasia, because it is totally dependent on the increased erythropoietin production stimulated by the anemia and ineffective erythropoiesis. By maintaining a normal hemoglobin level with high transfusion therapy one can suppress the stimulation of erythropoiesis and prevent these bony changes from occurring. A high transfusion regimen to achieve a minimum hemoglobin level of 10 g/100 mL is the currently accepted treatment modality for patients with transfusion-dependent homozygous β thalassemia. However, a consequence of high transfusion therapy is the development of iron overload, due to the large number of required blood transfusions.

Therefore, current therapy consists not only of high transfusions but, in addition, of active iron chelation, most effectively by use of the agent desferrioxamine. Unfortunately this agent is not effective orally, but must be given parenterally, and is most effective when administered continuously or semicontinuously. Thus, single intramuscular injections are not as effective as the current method of administration, which consists of subcutaneous infusion by a motor-driven, battery-operated pump. Most patients utilize such pumps twelve hours a day, usually overnight, for five to six days a week. With this type of regimen, it is possible to maintain iron balance. Long-term results of such therapy have begun to emerge and indicate a beneficial effect in prolonging the life of these patients, who previously would die in their late teens or early twenties from cardiac failure or arrhythmias due to iron overload in the myocardium.

A number of promising iron chelating agents that are orally effective are currently under study. It is to be hoped that in the next decade, some of these oral agents will be introduced into clinical practice and replace the inconvenient procedure of subcutaneous desferrioxamine infusions.

Molecular Basis

To understand the molecular basis of β thalassemia, knowledge of the structure of the β-globin gene is essential. The β-globin gene, like most other genes in our genome, does not encode its gene product in an uninterrupted linear fashion. The actual protein encoding region of the gene consists of three coding blocks or exons, separated by two intervening sequences, or introns.

The process of gene expression is complicated and includes a number of different steps **(Fig. 3)**. The gene is initially transcribed as a large pre-

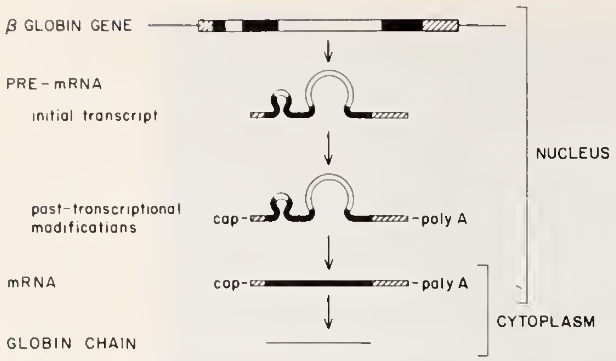

Fig. 3. Schematic representation of process of β-globin gene expression. *Reprinted* with permission from ref. 2.

cursor molecule containing intronic as well as exonic sequences. This initial transcript is then modified at both ends: poly(A) is added at the 3′ end and a methylated structure called the cap is added to the 5′ end. The poly(A) confers mRNA stability, and the cap is important for the interaction between the mRNA and initiation factors. The intervening sequences must then be excised and the coding sequences precisely ligated to one another to give the mature messenger RNA. This process is called splicing, and it is crucial for the production of functional mRNA. The mature messenger RNA is then transported from the nucleus to the cytoplasm, where it is translated into a globin peptide chain. In such a multistep process, many things can go wrong and, according to Murphy's Law, if anything can go wrong it usually will. The lesson that we have learned from thalassemia is that any step which can conceivably go wrong has in fact gone wrong in one family or another with β thalassemia. As a consequence, almost every possible defect in gene expression that could result in absent or diminished globin messenger RNA has been described in thalassemia. Thalassemia is the prototype of a genetic disorder characterized by a relatively homogeneous phenotype due to a highly heterogeneous number of different molecular defects.

Another noteworthy aspect of the process of gene expression is the existence of a number of critical sequences in the gene that determine the processes crucial for proper gene expression. In the promoter region of the gene, a number of consensus sequences, called boxes, such as the CCAAT box, CACCC box and TATA box, are important for the binding of the RNA polymerase and its associated transcription factors. There are also important initiation and termination signals. At the ends of intervening sequences there are crucial consensus sequences containing the dinucleotides, GT and AG, that are the signals for the sites of precise cleavage and excision of the intervening sequences. Finally, at the end of messenger RNA, there is another consensus sequence that is an important signal for the addition of the poly(A). In such a multistep process, a small change, such as a single nucleotide change in one of these critical sequences, can have a drastic effect on the accuracy and efficiency of gene expression and, thus, on the

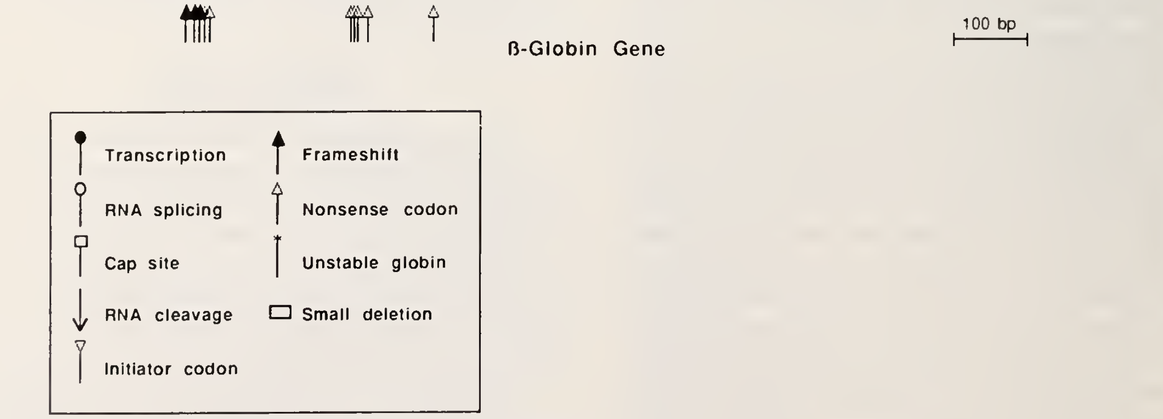

Fig. 4. Model of human β-globin gene showing sites and types of various mutations causing β thalassemia. *Reprinted* with permission from ref. 3.

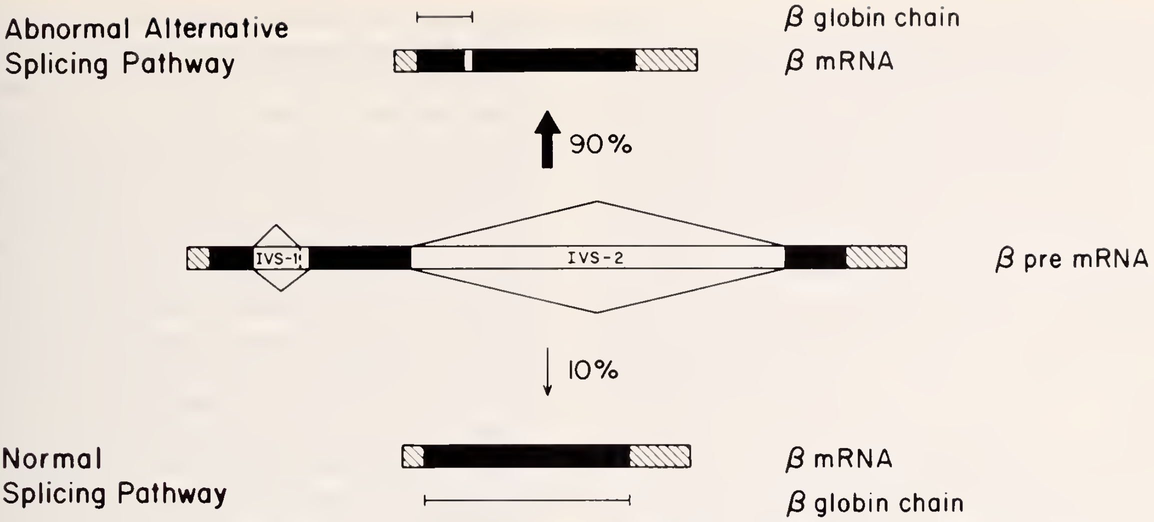

Fig. 5. Schematic representation of process of alternative splicing in β^+ thalassemia due to mutation in IVS-1 at position 110 (vertical broken line). *Reprinted* with permission from ref. 2.

quality and quantity of the encoded messenger RNA.

Over 90 different point mutations of the β-globin gene have been reported to cause β thalassemia (3) by a number of different categories of defects (**Fig. 4**). There are mutations in the promoter region of the β gene, in the conserved consensus sequences discussed above, that cause decreased transcription of the gene. There are a number of mutations in the coding blocks or exons themselves, either nonsense mutations, single-base substitutions that change a codon to a stop signal; or frameshift mutations, one- or two-base insertions or deletions that change the reading frame of the mRNA and result in premature chain termination when a new stop signal is encountered downstream. One of the more interesting categories of β thalassemia consists of the splicing defects due to mutations, either at the junctions of the intervening sequences or in the body of the intervening sequences, that result in abnormal processing of the precursor mRNA.

Illustrative examples of β thalassemia mutations are provided by molecular defects that are encountered in Mediterranean individuals. One such defect is due to a single-base change (C to T) that converts codon 39 for glutamine (CAG) to a stop codon (TAG). In this case, the messenger RNA encodes a truncated protein: instead of a 146 amino acid β-globin chain, translation of the mRNA results in the synthesis of an abnormal 39 amino acid nonfunctional peptide that is rapidly turned over and degraded. This β 39 nonsense mutation is the second most common cause of thalassemia in the Mediterranean population.

Another group of mutations are those that affect splicing. As previously discussed, the invariant dinucleotide GT is an important signal at the beginning of an intron that determines the precise site of cleavage of the precursor mRNA. There is a thalassemia mutation, a β^0 thalassemia mutation, where a single-base substitution, changing this GT to an AT, totally blocks the splicing of the large intervening sequence from the β pre mRNA; thus no normal β globin mRNA is produced and there is total absence of β globin chain synthesis.

The most common form of β^+ thalassemia in the Mediterranean basin has been shown to be due to an interesting and novel mechanism for abnormal gene expression: the creation of a new splicing signal in an intron that results in the processing of the majority of the β pre mRNA transcripts into abnormal mRNA molecules, only a minority of the pre mRNAs yielding normal β mRNA. The mutation is located at nucleotide 110 of IVS 1, 21 nucleotides upstream from the normal 3′ or acceptor AG of the first intron of the β-globin gene and consists of an A to G base substitution. This mutation creates a new acceptor AG, some 20 nucleotides upstream of the AG that is normally used, and in a sequence context that is similar, if not identical, to the normal 3′ splice site. As a result of this base change in an apparently unimportant part of the gene, a new signal is created that appears to be preferred over the normal signal by the splicing mechanism. The mutant pre mRNA can be spliced in one of two ways. It can be spliced normally; but this happens in only the minority of cases, approximately 10% of the time. For some reason, the new cryptic splicing signal created by the mutation is preferred and is used 90% of the time, giving a mutant messenger RNA that contains a small insert of intronic sequence (19 nucleotides long) that has a stop signal in it so the mRNA can only encode a truncated, abnormal β globin chain (**Fig. 5**).

In summary, studies of the molecular basis of thalassemia have demonstrated that the molecular cause of thalassemia is quite heterogeneous. Over 90 different mutations have been identified, yet the resulting phenotype is clinically and biochemically rather similar in most cases. The end result is the absent or decreased synthesis of β globin chains. As a consequence of that deficiency of β globin chains, excess α chains accumulate, damage the red cell, and lead to the clinical presentation of hemolytic anemia and ineffective erythropoiesis with marked marrow expansion. Despite the vast heterogeneity of molecular defects, the biochemical and clinical phenotype is quite similar because of the common denominator of absent or decreased synthesis of β globin chains, with resulting accumulation of excess α globin chains that cause the damage to the affected erythroid cells.

A number of additional general conclusions can be drawn from the results of studies on the molecular basis of β thalassemia, and these conclusions have implications for the prenatal diagnosis and future prospects for gene therapy of β thalassemia. A given mutation is generally found only within one racial group and not another. Thalassemia is quite common, not only in Mediterranean populations, but also in Afro-American and Asian populations. However, in these different racial groups one usually finds a different set of specific mutations. A given mutation also tends to be on the same chromosomal background in different individuals of the same racial group. If one determines polymorphisms in and around a β-thalassemic globin gene, one then has a clue to what mutation is likely to be present in that gene. Finally, a small number of mutations usually account for the majority of cases of β thalassemia in a given population. For instance, despite the overall high number of different β thalassemic mutations, over 90% of all the mutations observed in Mediterraneans can be accounted for by only six different molecular defects, the two most common being the nonsense mutation at codon 39 and the IVS 1 position 110 alternative splicing defect.

Prenatal Diagnosis

Information on the molecular basis of β thalassemia has been translated into new, highly effective, efficient, and accurate techniques for prenatal diagnosis. Initial procedures and approaches for the prenatal diagnosis of β thalassemia had to rely on obtaining fetal blood samples because the abnormal biochemical manifestation is restricted to red blood cells. This was usually carried out in the mid trimester by the procedure of fetoscopy, in which a needle was inserted into the uterine cavity and used to aspirate small amounts of blood from fetal blood vessels for analysis of globin chain synthesis. Although accurate and effective, this approach is not totally safe. Even in the best of hands, fetoscopy has a mortality and morbidity rate of approximately 5%. Knowledge of the nature of the β thalassemic mutations at the DNA level has now made possible the use of fetal DNA rather than fetal blood for the purpose of prenatal diagnosis. The source of fetal calls may be amniotic fluid obtained by regular amniocentesis in the mid trimester, or, as is now preferred, chorionic villi obtained by transcervical biopsy in the first trimester.

A technique that has revolutionized the ability to study mutations for any genetic disorder in small amounts of DNA is the polymerase chain reaction (4). The basic principle is to make synthetic oligonucleotide primers approximately twenty bases in length to either side of a region of interest of the gene, and to submit the DNA to repeated cycles of denaturation and in vitro replication by DNA polymerase using the primers as the site of initiation of DNA synthesis. One thus obtains geometrical amplification of the region of interest with the production, after 30 to 40 cycles, of over a million copies of the target sequence. Thus, starting with only 1 μg of total cellular DNA, one can obtain 1 μg of globin (or other) gene fragment for analysis.

There are two basic approaches for analyzing such amplified DNA to detect the presence of single-base mutations. One method is illustrated by the disorder in sickle cell anemia, in which there is a single-base substitution in codon number 6, changing a glutamine codon (GAG) to a valine codon (GTG). This single-base change also happens to change the recognition site for a restriction endonuclease, that is, an enzyme that cleaves DNA at a specific sequence. In normal DNA, there is a cleavage site for the enzyme *Mst*II that encompasses codon 6. In the sickle cell gene, that particular recognition sequence is abolished, so when mutant DNA is digested with the enzyme, a larger fragment is obtained than that obtained with normal DNA. If one amplifies this region of DNA as a small fragment of approximately 300 base pairs (bp), one can then test for the ability of that piece of DNA to be digested by *Mst*II. The

DNA fragment from a normal individual is completely cleaved into two subfragments of approximately 200 and 100 bp respectively. The DNA fragment of a patient who is homozygous for sickle cell disease remains totally undigested. Amplified DNA from an individual who is a heterozygous carrier for the sickle cell gene gives a pattern in which half of the DNA is uncleaved, and half is cleaved into the two smaller subfragments. Approximately 30% to 40% of the β thalassemia point mutations can be directly identified by the alteration of a restriction endonuclease site in amplified DNA.

However, the majority of mutations do not affect restriction sites; an alternative technique is available to detect such disorders. The approach consists of hybridization of the amplified DNA to allele-specific oligonucleotides (ASOs). The procedure uses two synthetic oligonucleotide probes that overlap the site of the mutation, one identical to the mutated sequence, the other to the normal sequence. The single-base difference in these synthetic oligonucleotides, ~20 bases in length, is located in the middle of the sequence and conditions can be established so that each oligonucleotide will hybridize only to its identical complementary sequence, and not to the sequence that is one base different. Amplified DNA from a normal individual will hybridize only to the normal probe and not to the mutant probe. DNA from a homozygous β thalassemic individual will hybridize only to the thalassemic probe and not to the normal probe. On the other hand, amplified DNA from an individual heterozygous for the β thalassemia mutation will hybridize equally well to both probes. Therefore, the technique of allele-specific oligonucleotide hybridization allows the detection of either homozygosity or heterozygosity for a given mutation and can be readily applied to the analysis of amplified DNA fixed to a filter.

The advantage of chorionic villus biopsy as a source of fetal cellular DNA is that the procedure can be done early in pregnancy, at eight to ten weeks of gestation, which is a much more acceptable time for family planning. The couple can make a decision much earlier in the pregnancy rather than having to wait until the second trimester, which is the time when amniocentesis is usually done.

In summary, the implications of molecular studies for prenatal diagnosis of β thalassemia are the following: DNA-based diagnosis, which is safer than fetoscopy, is feasible in the vast majority of cases, and has been greatly facilitated by the advent of the polymerase chain reaction. The procedure does require knowledge of the specific molecular defect in the parents, but with the speed and efficiency of the polymerase chain reaction, it should be possible to rapidly determine the mutations in a given couple at risk and thereby establish the appropriate procedures for prenatal diagnosis. DNA-based prenatal diagnosis of β thalassemia and other hemoglobinopathies is a current reality and is a direct extension and application of studies on the molecular basis of these disorders.

Prospects for Gene Therapy

The implications of studies on the molecular basis of β thalassemia for gene therapy of the disorder can be summarized as follows. A single effective approach to gene therapy would be the introduction of a functional β-globin gene into hematopoietic stem cells of the homozygous affected individual as a substitute for the defective genes. The transfer of a normal β-globin gene into the hematopoietic stem cells of an affected patient's bone marrow, and reinfusion of that transfected or transduced marrow, is one potential approach to gene therapy (5, 6).

A number of obstacles must be overcome before gene therapy becomes a reality. First, one needs to have regulated expression of the transferred gene. When one transfers a globin gene into hematopoietic stem cells, one wants it to be expressed only in the erythroid cells and not in the nonerythroid progeny of the stem cells. Also, one needs to have high levels of expression of the transferred gene. The amount of hemoglobin made in the red cell is considerable, and to adequately replace the deficient β-globin chain synthesis, one has to have very high levels of expression of the transferred globin gene. Finally, the gene must be transferred into the self-renewing or reconstituting stem cell in order to obtain long-lasting therapeutic results. A number of experiments indicate that if one transfers a human β-globin gene into the hematopoietic stem cells of a mouse, it will be expressed essentially only in erythroid cells and not in nonerythroid cells (7). Even though the transferred gene becomes integrated in a chromosomal environment different from that where it normally resides, it contains sufficient sequence in its immediate flanking DNA to confer erythroid cell-specific expression. Therefore regulated expression of transferred globin genes is not a real problem. On the other hand, the levels of expression of transferred globin genes have been disappointing. Experiments in mice (7) and in tissue culture cells usually result in only approximately 5% to 10% as much expression of the transferred gene as that of the endogenous globin gene. Such a level would not be enough to reverse the defect in β thalassemia. One needs to achieve a level of expression from the transferred globin gene(s) that is nearly as high as that of a normal endogenous globin gene.

Recently, there has been important progress in the development of strategies to increase the amount of expression of transferred globin genes to levels that would be therapeutically effective. The advance that should contribute to achieving high levels of globin gene expression following gene transfer is the recent discovery of interesting sequences in the β-globin gene cluster that are located far upstream from the globin genes and were initially identified as hypersensitive sites to digestion by DNase I (8). The importance of these sequences was first suggested by the finding of a number of mutations in which the β-globin gene itself is structurally normal but not expressed when located on a chromosome that carries a deletion of these sequences. Four such deletions have so far been identified and are associated with the phenotype of γδβ thalassemia. These deletions remove different amounts of the β-globin gene cluster, the most striking being Hispanic γδβ thalassemia, in which all the β-like globin genes are intact but silent due to a ~30 kb deletion involving three of the four hypersensitive sites (9). When DNA sequences containing these DNase I hypersensitive sites are linked to a β-globin gene that is used to produce transgenic mice, the level of expression of the transferred β-globin gene is virtually equal to that of the endogenous gene (8). These sequences have been called the LCR, or locus control region. The LCR confers high levels of erythroid-specific expression to transferred β-globin genes, in a copy-dependent and position-independent manner, that is, the level of expression is proportional to the number of copies of the gene that are transferred and is uniformly high irrespective of the chromosomal site of integration of the transferred gene(s). The DNA sequences that are critical for the functional activity of the LCR have been localized to a small region of DNA surrounding the DNase I hypersensitive sites, so it should be possible in the future to insert these sequences into retroviral (or other) gene therapy vectors to obtain near normal levels of expression of transferred β-globin genes.

The most likely approach to gene therapy for β thalassemia will involve the use of retroviral vectors because of the efficiency with which such vectors can introduce genes into hematopoietic (and other) cells (5, 6). One concern with such vectors is safety and the possibility that the disabled vector DNA initially rendered incapable of producing infectious viral particles could recombine with normal viral sequences and lead to chronic productive viremia, with the possibility of insertional mutagenesis leading to malignant transformation. However, a number of systems have been developed that greatly reduce the chance of such viral recombination, although insertional mutagenesis is still remotely possible with only a single cycle of retroviral introduction and chromosomal insertion into hematopoietic stem cells. Another issue in the use of retroviral vectors is the feasibility of retroviral transfer into the pluripotential or reconstituting hematopoietic stem cells. Because retroviral integration requires one cycle of cell division, and pluripotential stem cells are predominantly in the resting or G_0 phase of the cell cycle, the frequency of retroviral infection (or transduction) of pluripotential stem cells is much lower than that of more mature, and therefore shorter lived, hematopoietic progenitor or precursor cells. However, the prestimulation of target marrow cells with various combinations of hematopoietic growth factors has greatly increased the frequency of successful stem cell transduction (10).

The general approach to gene therapy would consist of the aspiration of bone marrow from the affected patient followed by the in vitro exposure of the marrow cells to defective retroviral particles, containing a copy of a normal β-globin gene, that have been modified so their genetic material (RNA) lacks the necessary information to permit viral replication. After entry into the marrow cells, the reverse transcriptase enzyme of the viral particle will make a DNA copy of the retroviral genome, which will then become integrated in a random fashion within the chromosomal DNA of the marrow cells. The transduced cells are then reinfused intravenously into the patient, where they will hone to the bone marrow space and continue to proliferate normally. The transferred β-globin gene should be expressed exclusively, and it is hoped at a high level, in the erythroid cell progeny of the transduced stem cells.

Although actual attempts of long-term (that is, stem cell) gene therapy for β thalassemia are many years away, short-term gene therapy for another genetic disorder, adenosine deaminase deficiency, has already been initiated by means of repeated transduction and reinfusion of peripheral blood lymphoid cells (6).

Summary and Conclusions

Review of the pathophysiology and molecular basis of β thalassemia reveals that an extremely heterogeneous group of molecular defects can give rise to a relatively uniform clinical and hematological phenotype that is primarily the result of the excess of free α-globin chains that accumulate in the face of absent or markedly reduced β-globin chain synthesis. Despite the molecular heterogeneity, it has been possible to establish highly accurate and efficient DNA-based prenatal diagnosis for β thalassemia. Important progress is also being made in the area of gene therapy for β thalassemia.

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Current Concepts of Systemic Necrotizing Vasculitis

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The primary idiopathic vasculitides are generally distinguished from one another by the size of the vessel involved, the organ systems affected, and the pathologic presence or absence of a granulomatous lesion (1). Descriptive classifications (outlined briefly in ruled box) based on these features have been the subject of previous reviews (2–4). Since the classic original description of periarteritis nodosa by Kussmaul and Maier (5), it is now appreciated that notable overlap exists within the clinicopathologic spectrum of systemic vasculitis (6). The preferable term, systemic necrotizing vasculitis (SNV), refers to a group of disorders characterized by an inflammatory infiltrate in the wall of small to intermediate-sized muscular arteries associated with clinical disease from resultant ischemia or infarction of the kidney, gut, nerve, myocardium, lung, skin, and genitourinary tract (6).

The histopathology of SNV evolves over time. Early lesions are characterized by a panarteritis with infiltrating polymorphonuclear leukocytes (PMN), fibrinoid necrosis, endothelial cell injury, and thrombosis. Mononuclear cells with intimal proliferation typify the chronic stages. There is a predilection for vascular injury to occur with a focal distribution, often at sites of arterial bifurcation, producing microaneurysmal dilatation (7, 8).

Etiopathogenesis

The current understanding of the pathogenesis of SNV is based on the serum sickness model of immune complex disease in both animal models and humans (9, 10). In this paradigm, circulating immune complexes form in the presence of antigen excess and, modulated by physical factors such as local temperature, turbulence, size, and electrical charge, deposit in the vascular wall (9 11). In most forms of vasculitis the "triggering" antigen is unknown; however, the association of specific infectious agents, neoplastic disorders and drugs with SNV provides insight for the pathogenesis of these predominantly idiopathic syndromes. Hepatitis B has been noted to occur in from 20% to 30% of patients with polyarteritis nodosa (12). The use of more sensitive assays that employ monoclonal antibodies against the hepatitis B surface antigen, or molecular probes for viral DNA in the peripheral blood lymphocytes of affected patients, has recently been reported to increase the identification of hepatitis B infection in vasculitis patients who were previously seronegative with standard polyclonal assays (13) Using these techniques, the prevalence for hepatitis B seropositivity in polyarteritis was 75% (13). Additional evidence for infectious agents has included SNV in individuals with cytomegalovirus (14), parvovirus (15), human immunodeficiency virus-1 (16), varicella-zoster (17), Epstein-Barr virus (18), rubella (19), *Borrelia burgdorferi* (20), the recently identified hepatitis C (21), and SNV as a sequela of acute serous otitis media (22).

The best model of neoplastic disease associated with SNV is hairy cell leukemia (23). Vasculitis has also occurred in association with carcinoma of the colon, nasopharynx, prostate, kidney, breast, cervix, and lung; melanoma; and pheochromocytoma (24). Penicillins, sulfon-

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amides, phenytoin, and heterologous antiserum (most recently antithymocyte globulin) are among the most important causes of drug-related vasculitic disease (4, 10).

Complement activation by in situ immune complexes generates cleavage fragments with important biologic activities that mediate chemotaxis of PMN (C5a) and degranulation of basophils and mast cells (anaphylotoxins C3a, C4a, and C5a). Histamine release by these fragments, histamine-releasing factors from infiltrating mononuclear cells (25), or potentially anti-IgE autoantibodies (26) promote localization of immune complex material along the endothelial basement membrane (27). Further recruitment of PMN is likely to be augmented by leukotriene-B-4, platelet-activating factor, and the neutrophil-activating peptides-1 and -2 (28, 29). Cytokines elaborated by infiltrating mononuclear cells increase the expression of adhesion proteins on the endothelial surface (30). These include endothelial-leukocyte adhesion molecule-1, which is induced after stimulation with interleukin (Il)-1 and tumor necrosis factor (TNF)-α, and intercellular adhesion molecule-1, present on resting endothelial cells and up-regulated by Il-1, TNF-α, and interferon-γ.

Both humoral and cellular immunity appear to be important in the generation of pathologic variants of SNV. Granuloma formation may be related to a T-cell response to autoantigens and cytokine production. In that regard, Il-1, TNF-α, Il-6, and interferon-γ, which are influential in the generation of granulomas, presumably play a pivotal pathogenetic role in Churg-Strauss vasculitis and Wegener's granulomatosis (31). Furthermore, Il-5, crucial to eosinophil growth and activation, may be critical to the eosinophilia and tissue injury of Churg-Strauss vasculitis (32). Granulocyte-macrophage colony-stimulating factor, a product of T cells and macrophages, has recently been observed to produce lesions of necrotizing vasculitis at sites of cutaneous injection (33). Il-4 activates monocytes and macrophages to become giant cells and may be central to the production of vasculitis-specific antineutrophil autoantibodies (see below).

As PMN are recruited by chemoattractants and secured to the endothelium by adhesion molecules, they release proteases and oxygen radicals that degrade basement membrane components and produce vascular injury. The exposure of basement membrane permits activation of the clotting and fibrinolytic pathways via Hageman factor (34). The presence of Il-1 and TNF-α, which increase tissue thromboplastin and decrease plasminogen activator release from endothelial cells, creates a prothrombotic milieu favoring occlusive disease (35, 36).

Classification Schema for Vasculitis

I. Large vessel arteritis
  - Takayasu's arteritis
  - Giant cell arteritis

II. Medium and small vessel systemic necrotizing vasculitis (SNV)
  - Polyarteritis nodosa (PAN) group
    - Classic PAN
    - Churg-Strauss (allergic granulomatosis)
    - "Overlap"
    - Microscopic polyarteritis
    - Kawasaki disease (infantile PAN)
    - Amphetamine induced SNV
    - SNV associated with Crohn's disease
    - SNV associated with infection
    - SNV associated with neoplasm
    - SNV associated with the connective tissue disease
    - Localized PAN
      - Skin
      - Appendix
      - Gallbladder
      - Kidney
      - Lung
      - Mesentery
      - Uterus
      - Breast
      - Epididymis
      - Testis
  - Wegener's granulomatosis
  - Lymphomatoid granulomatosis

III. Small vessel arteritis/venulitis
  - Hypersensitivity vasculitis/leukocytoclastic vasculitis
    - Infection
    - Drug/serum sickness
    - Neoplasm
    - Connective tissue disease
    - Essential mixed cryoglobulinemia
    - Henoch-Schönlein purpura

Clinical Disease

The majority of patients with SNV will have constitutional features such as fatigue, weight loss, fever, arthralgias, and myalgias. The prevalence of specific target organ involvement varies with each vasculitic syndrome. Necrotizing vasculitis can be subdivided into a number of syndromes, all characterized by clinical overlap: classic polyarteritis nodosa (5); the Churg-Strauss variant of allergic granulomatosis in individuals with a background of atopic disease, asthma, and eosinophilia (37); overlap vasculitic syndromes

(6); microscopic polyarteritis with prominent renal disease that resembles that seen in Wegener's granulomatosis (38); vasculitis associated with amphetamine abuse (4); necrotizing vasculitis with Crohn's disease (39); Wegener's granulomatosis; and the systemic vasculitis associated with connective tissue or immunologically mediated disorders. The latter include systemic lupus erythematosus, rheumatoid arthritis, Sjögren's syndrome, Behçet's disease, relapsing polychondritis, Cogan's syndrome, Buerger's disease (thromboangiitis obliterans), and, rarely, systemic sclerosis (4, 40–42).

Renal disease is the most common feature of classic polyarteritis (70% or greater) and is the result of vasculitis, glomerulonephritis, or hypertension (4). Aneurysms of the renal circulation may rupture, leading to spontaneous perirenal hemorrhage and hypotension (43). Recent data indicate that even when end-stage renal disease develops (often cited as the most common cause of death in polyarteritis nodosa), the overall survival is quite good and comparable to that of age-matched control patients with non-diabetes-associated renal disease (62% at 36 months). Furthermore, 10% of patients have been reported to recover significant renal function and discontinue dialysis (44).

Neurologic involvement is common to all forms of SNV. Peripheral neuropathy occurs in up to two-thirds of patients, usually in the form of a diffuse sensorimotor polyneuropathy; however, mononeuritis and isolated cutaneous neuropathies may develop (45). The most common sites are the peroneal, sural, radial, ulnar, and median nerves (45). The most frequently identified cranial neuropathies are cranial nerves II, VII, and VIII (46). Central nervous system disease (40%) is manifested by diffuse (encephalopathy, seizure) or focal (cerebrovascular accident) abnormalities.

Gastrointestinal disease in patients with SNV includes ischemia and infarction of the bowel, hepatobiliary tree, pancreas, and appendix (47–49). Clinically, individuals initially have fever, abdominal pain, gastrointestinal bleeding (upper, lower, or intra-abdominal), peritonitis, and intrahepatic hemorrhage (47–49).

Pulmonary infiltrates, characteristic of Churg-Strauss vasculitis and Wegener's granulomatosis, are typically not seen in classic polyarteritis but may be a manifestation of overlap SNV and microscopic polyarteritis. Pleural effusions should suggest infection until proven otherwise. Cardiac disease is characterized by congestive heart failure, fibrosis and pericarditis (Churg-Strauss), myocardial infarction and arrhythmias (classic polyarteritis nodosa), and coronary artery aneurysms (Kawasaki disease) (46, 50, 51).

The cutaneous lesions of SNV are pleomorphic and not distinct for any individual syndrome. These include palpable purpura, urticaria, ulcers, livedo reticularis, and subcutaneous nodules (52).

Testicular vasculitis, although common at autopsy (up to 86%), is symptomatic in only 2%–18% of patients (53). Isolated lesions of necrotizing vasculitis (without associated systemic disease) involving the epididymis or testis have been rarely reported and may be asymptomatic or mimic neoplastic disease (53, 54).

Diagnostic Studies

The laboratory approach to the diagnosis of SNV has changed dramatically over the past few years. The observation that antineutrophil cytoplasmic autoantibodies (ANCA) are both sensitive and specific for certain subsets of necrotizing vasculitis has been critical to the diagnosis and management of patients with suspected SNV. The ANCA represent a new class of autoantibodies directed against myeloid lysosomal enzymes. Using indirect immunofluorescence on ethanol-fixed polymorphonuclear leukocytes, two patterns have been identified (55). The classic pattern is cytoplasmic (c-ANCA), which has recently been demonstrated to be against a 29-kDa serine protease (proteinase 3) located in azurophilic (primary) granules and to a lesser extent on the plasma membrane of PMN and monocytes (56). Antibodies with a perinuclear pattern (p-ANCA) are against myeloperoxidase and elastase, also in the primary granules (55, 57). p-ANCA is found with the greatest frequency in patients with disease confined to the kidney (crescentic glomerulonephritis), whereas c-ANCA positivity is greatest in patients with granulomatous lung disease (58).

The sensitivity of the ANCA is greatest in Wegener's granulomatosis, where they have been noted in a prevalence of 50%–96% (59, 60). The sensitivity is as high as 100% during active disease, 70% for disease limited to the respiratory tract, and 30% during remission (57). The specificity for Wegener's is also very high (90% or greater) (60).

c-ANCA has also been noted in patients with microscopic polyarteritis, a necrotizing vasculitis involving the kidneys with pathology that resembles that seen with Wegener's (61), and Kawasaki disease. Antimyeloperoxidase antibodies have been identified in idiopathic crescentic glomerulonephritis, Churg-Strauss, Takayasu vasculitis, and less often in systemic lupus erythematosus, relapsing polychondritis, Behçet's disease, Henoch-Schönlein purpura (IgA isotype), inflammatory bowel disease, and primary sclerosing cholangitis (57, 62–64). In addition to their central role in the evaluation of patients with SNV, current evidence supports a pathogenic function for ANCA. The ANCA-specific antigens are translocated to the surface of cells following exposure to cytokines such as TNF-α. Subsequent binding of ANCA to these primed PMN has demonstrated release of oxygen radicals and proteases in vitro (65). The recent finding that ANCA may be produced in the respiratory tract of patients with Wegener's provides additional support for their potential pathogenetic role (66).

Antineutrophil autoantibodies directed against the 29-kDa serine protease and myeloperoxidase are predominantly of the IgG1 and IgG4 isotypes (67). IgG4 is produced after recurrent stimulation and is dependent on T-cell production of Il-4, which regulates the isotype switch from IgG1 to IgG4 (68). It is therefore likely that, as a result of an antigen-driven T-cell response in Wegener's, Il-4 is generated and is important to the synthesis of ANCA, which subsequently activate PMN and contribute to tissue injury.

Recent studies have suggested that the promyelocytic cell line HL60 is useful for differentiating antineutrophil antibodies from antinuclear antibodies (ANA) (69). These cells are potentially helpful in distinguishing a false positive p-ANCA from an ANA; however, because of phenotypic drift during cell passage, ANCA-specific antigens may be lost (70).

In addition to the ANCA, other autoantibodies have been reported to be present in patients with SNV. None, unfortunately, have the same degree of sensitivity or specificity, but may offer insight into the mechanisms of tissue injury. Antiendothelial cell autoantibodies, identified predominantly in patients with small vessel vasculitis, have been reported in Kawasaki disease (71). The antiphospholipid antibodies are primarily associated with thromboembolic disease and a noninflammatory vasculopathy rather than a true vasculitis; however, there is some evidence for the latter as well (72, 73). Antilamin antibodies are a rare group of autoantibodies that have been found in association with small vessel vasculitis (74). The Ro (SS-A) antigen, associated with primary Sjögren's syndrome and systemic lupus, has been linked to cutaneous vasculitis in Sjögren's (75). Anti-IgE autoantibodies are of theoretical value in understanding the mechanisms of histamine release from basophils and mast cells and have been identified in individuals with vascular lesions such as systemic lupus and scleroderma (26, 76), as well as in some patients with urticarial vasculitis (77). Unidentified precipitins against rabbit thymus extract not found in other connective tissue diseases or polyarteritis nodosa have been identified in rheumatoid vasculitis (78).

Visceral angiography is useful in the evaluation of SNV and demonstrates microaneurysms in 30%–60% of patients (79). These are most often present in the renal circulation, the celiac axis, and the superior mesenteric artery, necessitating study of each of these vascular beds during arteriography (4, 46). Unfortunately, the finding of microaneurysms is nonspecific, and they may be a feature of disorders that mimic SNV, such as atrial myxoma, endocarditis, fibromuscular dysplasia, and pseudoxanthoma elasticum (4). Furthermore, caution should be exercised in performing angiography in view of reports of dye-associated acute renal failure in the setting of SNV (80).

Ultimately, the most conclusive diagnosis is dependent on demonstrating the lesion of SNV histologically. In general, biopsy sites should be selected as determined by the clinical manifestations, and tissue should be obtained from the most easily accessible and involved organ. Cutaneous lesions will often demonstrate vasculitis; however, this does not necessarily correlate with the presence of visceral involvement. Nevertheless, in an individual with multisystem disease and vasculitic skin lesions, additional tissue need not be obtained. Abnormal neurophysiologic studies correlate well with the ability to define vasculitis by sural nerve biopsy (81). Although the yield from muscle biopsy is traditionally greatest when painful areas are sampled, blind biopsies have also been reported to be useful (82). Recent reports of rectal biopsies demonstrating necrotizing vasculitis may suggest an alternative "blind" site in patients with diffuse systemic disease in whom a SNV is suspected clinically (83). Renal biopsies most often demonstrate glomerulonephritis in patients with SNV, and microaneurysms are a potential source of intrarenal hemorrhage; however, percutaneous needle biopsy by an experienced individual may also be useful (84). In Wegener's granulomatosis, recent studies have demonstrated diagnostic nasal biopsies in as many as 53% of patients, emphasizing the need

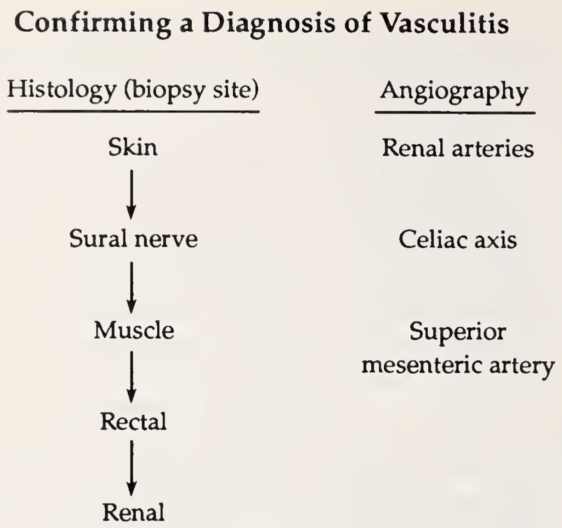

Fig. Proposed diagnostic approach to biopsy and angiography in systemic vasculitis. The choice of a blind biopsy or visceral angiography will often depend on the clinical presentation and risk-benefit analysis for a particular patient.

for obtaining tissue specimens larger than 5 mm (85). A suggested approach to biopsy is outlined in the **Fig.**

Differential Diagnosis and Therapy

A number of clinical syndromes and diseases may mimic SNV and must be differentiated from it. In that regard, the recent criteria established by the American College of Rheumatology (86) will be helpful in distinguishing SNV from clinically similar entities and allow standardization of patients entered into prospective clinical trials. Embolic disorders, in particular, may masquerade as vasculitis. The syndrome of cholesterol or atheroemboli presents with vasculitic-appearing skin lesions, livedo reticularis, renal insufficiency, and eosinophilia (87). Similar cutaneous and renal findings may occur in the syndrome of left atrial myxoma (88). Thrombotic thrombocytopenic purpura is a multisystem syndrome characterized by fever, renal disease, microangiopathic anemia, thrombocytopenia, and central nervous system abnormalities that has been reported to be associated with microaneurysms (4). Finally, the anticardiolipin or antiphospholipid syndrome is a thromboembolic disorder associated with cutaneous and visceral infarction.

Corticosteroid and immunosuppressive agents provide the principal therapy in these diseases. In an open trial with cyclophosphamide (2 mg/kg per day) for severe necrotizing systemic vasculitis, dramatic results were reported in 16 patients with progressive disease in spite of high doses of corticosteroids (89). Although the use of cytotoxic agents has had a dramatic impact on the course of SNV compared to historical controls, it should be emphasized that there have been very few attempts at prospective controlled studies. Furthermore, acute leukemia following cyclophosphamide therapy for PAN stands as a reminder of the significant toxicity of alkylating drugs (90). A recent multicenter, prospective, randomized study examined the risks and benefits of corticosteroids and plasma exchange with and without cyclophosphamide for PAN and Churg-Strauss vasculitis in 71 patients (91). In this trial there were more withdrawals due to lack of efficacy in the group without cyclophosphamide, and more related to toxicity in the cytotoxic group. Although the ten-year cumulative survival was no different in either group (72% versus 75%), relapse occurred statistically less often in the patients receiving cyclophosphamide. Newer, and more novel, immunomodulatory approaches to therapy have included monoclonal anti-CD4 antibodies (92) and high-dose intravenous immunoglobulin (93).

The use of corticosteroids for the treatment of SNV has recently been challenged by Conn et al. (94). This hypothesis suggests that although steroids may blunt much of the acute inflammatory process, platelet thromboxane may not be inhibited in vivo. As a result, platelet activation may lead to intimal proliferation and luminal occlusion on the basis of a noninflammatory vasculopathy.

At present, no conclusive data exist regarding the benefit of different immunosuppressive agents alone or in combination with other modalities. Indeed, as others have noted, a large multicenter study utilizing recently established criteria for PAN and related disorders will be required to help define optimal therapy for SNV (95).

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The Global Impact of Penicillin:

Then and Now

GENE H. STOLLERMAN, M.D.

NINETEEN NINETY-ONE was the 50th anniversary of the introduction of penicillin into medical practice, thanks largely to Ernst Chain's gift for masterminding its industrial production (1).

In the Beginning. In 1941, those of us in medical school were soon to become appalled and enthralled by the great scourges of young hearts, rheumatic fever, bacterial endocarditis, and syphilis. Only for the last of these scourges was treatment available, and that consisted only of arsenicals taken for prolonged periods.

In 1944, at the peak of World War II, when I began house staff training at the Mount Sinai Hospital in New York, penicillin was a precious military priority. Small supplies were made available to leading authorities for clinical investigation. Among these were George Baehr, Chief of Medicine, who shared with Emanuel Libman and other Sinai greats an international reputation in the study of bacterial endocarditis. Baehr and Gregory Shwartzman set up a laboratory under Stanley Schneierson that was among the earliest to assay the sensitivity of bacteria to penicillin tissue levels following various treatment regimens. We, the house staff, were the labor crew for the study of the earliest treatment of subacute bacterial endocarditis (SBE) (2).

Repository Penicillins

When I returned from military service i 1947 to become George Baehr's chief resident, re search on penicillin treatment of SBE was in ful swing. Ed Roston, my co-chief resident, and were given the job of testing the newly appearin repository penicillins, specifically procaine peni cillin G.

Levels and Duration of Therapy. From th studies of Harry Eagle (3) **(Fig. 1)**, it was appar ent that low levels of penicillin were all that wer needed to kill sensitive organisms such as th group A *Streptococcus* (GrAS). The time require to kill virtually all organisms in a cultur reached a maximum in but a few hours at a pen icillin level as low as 0.01 U/mL. No greater con centration of penicillin could increase the rate o killing when the organism was in its maxima growth phase. For a slow-growing organism o similar sensitivity, such as *Treponema pallidum* the maximum rate of killing also occurred at o below a level of 0.01 u/mL, but the time require for killing an organism that multiplied every sev eral hours instead of every 20 minutes was muc greater.

It was clear, then, that long duration of ther apy at low levels was what was needed. Th emerging repository penicillins could provide jus those prolonged low levels without continuous in travenous therapy or frequent bolus injections.

Another critical principle of successful peni cillin therapy was established by the studies o Dr. Barry Wood (4) **(Fig. 2)**. When penicillin wa added to a growing culture of *S. pneumoniae* dur ing the log phase of its growth, the organism were rapidly killed. If, however, penicillin wa added when the culture stopped growing, the or ganisms were not killed. When pneumococci wer

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inoculated into pus which prevented their growth, penicillin did not kill until the infected pus was reinoculated into fresh culture medium.

The lesson was clear for the treatment of bacterial endocarditis. Given a sensitive organism in the active phase of growth, a modest level of penicillin should suffice, but the duration of therapy would have to exceed the time required for an abscess in a valve to clear itself of dormant though potentially still viable organisms.

SBE is an infection in which host defenses are virtually ineffectual. The outcome is a contest between antibiotic and parasite. An in vitro test became our experimental model to determine at what level of antibiotic we could expect a bactericidal rather than a bacteriostatic effect. It already had been determined that bacteriostatic antibiotics would not cure SBE. Some organisms, in fact, could be efficiently eliminated only by a two-pronged antibiotic attack, one that became available with the introduction of streptomycin and other aminoglycosides.

This in vitro determination of bacteriostatic vs. bacteriocidal actions of antibiotics became known as the "Schlichter" test (5). The minimum levels required to *kill* an organism became known as the minimum bactericidal concentration (MBC), and the minimum levels required to *inhibit* growth, the minimum bacteriostatic concentration (MIC). When an organism was killed by penicillin at the same level as it was inhibited (MBC/MIC = 1) it was judged to be a strain whose destruction was close to assured in SBE therapy. When, however, a marked difference occurred between MIC and MBC, one could anticipate a high risk of relapse unless combined therapy with two bacteriocidal antibiotics eliminated the disparity. The latter situation was encountered most often in the treatment of bacterial endocarditis due to enterococci and staphylococci, but rarely with the *viridans* streptococci and never with group A streptococci or pneumococci.

Armed with these principles, Ed Roston and I (5) conducted a clinical experiment **(Table 1)** using relatively small doses of procaine penicillin G for the treatment of SBE due to sensitive strains of *Streptococcus viridans.* To effect a cure we needed only to sustain blood levels of approximately 1.0 u/mL for 6–7 weeks by giving procaine penicillin twice daily in doses ranging from 450,000 to 600,000 units (6).

Cellular Action of Penicillin

By the 1950s, the mode of action of penicillin at the cellular level had become clearer. Interference with cell-wall synthesis could be readily demonstrated in some strains of *E. coli.* When

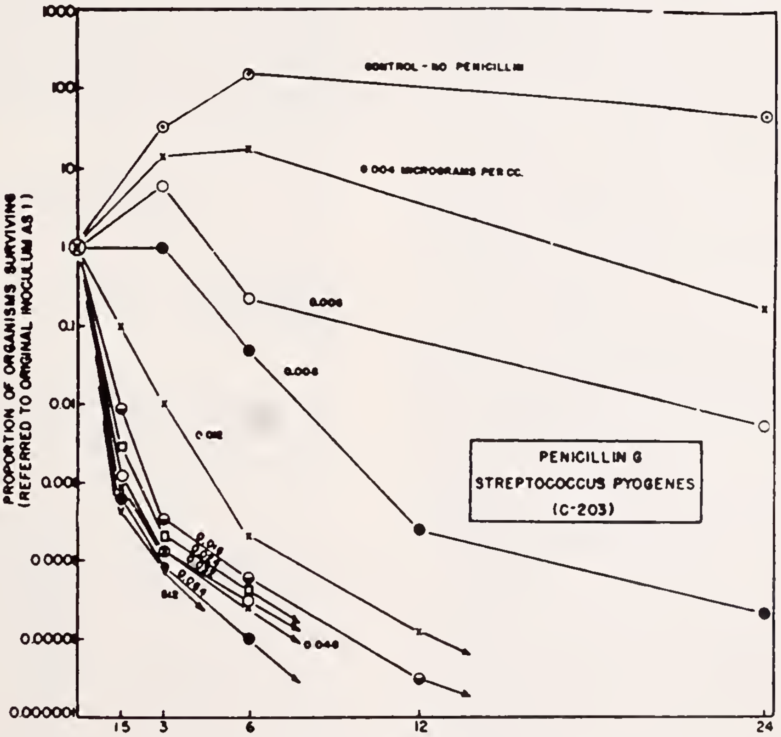

Fig. 1. Rate of killing of growing cultures of group A streptococci at varying concentrations of penicillin G (Ref. 3).

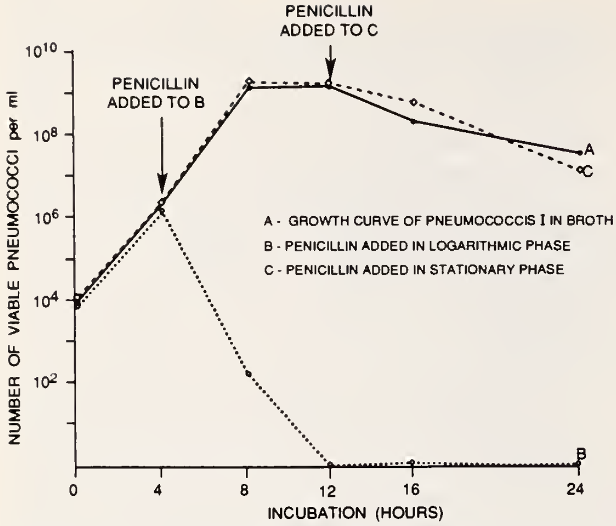

Fig. 2. Rapid killing of *S. pneumoniae* by penicillin G when added to culture during log phase of growth, in contrast to lack of significant killing when added during stationary phase of growth (Ref. 4).

grown in penicillin, synthesis of the cell wall was inhibited, but the organism's inner membrane-bound protoplast could survive with variable robustness against osmotic lysis, especially when cultured in media of high osmotic concentration. The cellular metabolic basis for penicillin's action, meanwhile, was rapidly elucidated by the discovery of the inhibition by penicillin of bacterial cell wall synthesis (7). Cross-linking of the muramic acid-N-acetyl glucosamine polysaccharide chains of the cell wall by glycopeptides was shown to be disrupted by penicillin with consequent dissolution of the cell wall.

Penicillin Resistance. Further study has revealed that gram-positive organisms have in their cell membranes certain proteins that are important in the regulation of normal cell-wall lysis and synthesis and are necessary for the growth, division, and remodeling of the bacterial wall. The affinity of penicillin for these so-called penicillin-binding-proteins (PBP) is essential for penicillin's antibiotic effect (8). Organisms very sensitive to penicillin lyse and explode. The ominous defense that certain bacteria can develop by producing beta lactamases that destroy penicillin have made treatment of certain strains of staphylococci, among others, notoriously difficult, requiring, first, the development of methicillin and its congeners for protection of the beta lactam ring of penicillin against beta lactamases, and later, alternatively, the introduction of the cephalosporins. Methicillin resistance, however, has now emerged in strains that have mutated to produce in their cell membranes PBPs of frighteningly low penicillin affinity. They are thus "metabolically resistant," in contrast to resistance resulting from beta lactamase production.

The cell walls of gram-negative organisms have a more complex structure. An outer cell membrane makes penetration of the cell wall by penicillin possible only through surface porins, or channels. Numerous genetically polymorphic PBPs with varying affinity for penicillin are either present or are inducible, so that resistance to penicillin can rapidly emerge by numerous mechanisms.

Bacterial Adherence. Fortunately, with a few rare exceptions, gram-negative organisms do not stick to heart valves or endocardium in the course of bacteremia. Adherence of streptococci has been shown by my former colleagues, the late Edwin Beachey and Itzhak Ofek (9), to be due to surface lipoteichoic acids. GrAS adhering to a buccal mucosal cell (**Fig.** 3) was shown to be due not to the surface M protein, as we originally thought, but to the closely associated membrane lipid, lipoteichoic acid. Lipoteichoic acid is interwoven with streptococcal M protein, but its fatty acid terminal protrudes from the cell membrane and forms the ligand that binds to fibronectin on the surface of most mucus membranes, and probably on scarred heart valves as well (10). Binding by various lipoteichoic acids occurs with the gram-positive organisms that cause SBE: streptococci, pneumococci, staphylococci, and enterococci. The treatment of SBE due to methicillin-resistant staphylococci, especially adherent to prosthetic valves, has now become something of a therapeutic nightmare.

Penicillin Therapy of Sensitive Organisms

Rheumatic Fever. A more pleasant topic is the impact of penicillin on group A streptococci

TABLE 1

Early Success in Procaine Penicillin RX of Subacute Bacterial Endocarditis due to S. viridans

Case	Pen. sens.	Days Rx	Daily dose IM	Penicillin levels Mean	Penicillin levels Range
M.K.	0.1	56	450,000 BID	1.5	0.2–2.0
A.K.	0.14	24	450,000 BID	1.1	0.5–1.3
L.C.	0.2	42	600,000 BID	1.45	0.6–2.0
S.N.	0.05	42	450,000 BID	1.0	0.8–1.3

Adapted from ref. 6.

and on *T. pallidum.* In 1950, the Wyeth Co. developed benzathine penicillin G (Bicillin). At the time, I was director of Irvington House, a research and treatment center for children with rheumatic fever and rheumatic heart disease at Irvington-on-Hudson, NY. Because of my interest in long-acting penicillins and the prevention of rheumatic fever, I was contacted to study Bicillin's potential for human use. To our astonishment, blood levels following a single intramuscular dose were shown to outlast, by far, all other forms of repository penicillin salts. In fact, one dose of 600,000 units, as Jerome Rusoff and I first reported in JAMA in 1952 (11), persisted in blood samples for 10 days at very low levels (**Fig.** 4), but within the range of sensitivity of two exquisitely penicillin-susceptible organisms, group A *Streptococcus* and *T. pallidum.* Moreover, with monthly intramuscular doses of 1.2 million units, we protected rheumatic subjects virtually completely against recurrent rheumatic fever.

Syphilis. Although I hankered to attack syphilis as well with what seemed to be a single-injection treatment, I had to be satisfied with reporting my results to one of my mentors, Dr. Harry Eagle at the U.S. Public Health Service Venereal Diseases Research Laboratory (VDRL). He promptly confirmed our prolonged blood level data and the U.S. Public Health Service went pell-mell after syphilis. The impact on syphilis was spectacular. Early VDRL data (**Table 2**) reveal that primary, secondary, and tertiary syphilis were cured with an effectiveness equal to that of any alternative penicillin regimen. One dose of 2.4 units intramuscularly was all that was necessary to cure primary or secondary syphilis, and three weekly doses sufficed for tertiary syphilis, with some rare exceptions. Some of us will recall the marvel of curing even a huge gumma with modest doses of penicillin. Those of us who were once authoritative in the treatment of syphilitic heart disease are now rarely solicited for our expertise. Although syphilis still lurks all too frequently in the morass of current sexually transmitted infection, and runs wild in patients with AIDS, the organism remains eminently treatable with low-dose penicillin regimens.

Rheumatic Fever and Streptococcal Pharyngitis. The studies at Irvington House that I initiated with Bicillin (12), so faithfully continued and completed by my colleagues Angelo Taranta, Harrison Wood, and Alvan Feinstein (13), are summarized in **Table 3**. Not only has monthly benzathine penicillin been the most effective regimen for preventing rheumatic recurrences, but its study has enabled us to learn the natural history of rheumatic heart disease when subsequent streptococcal infection is fully controlled in the rheumatic host.

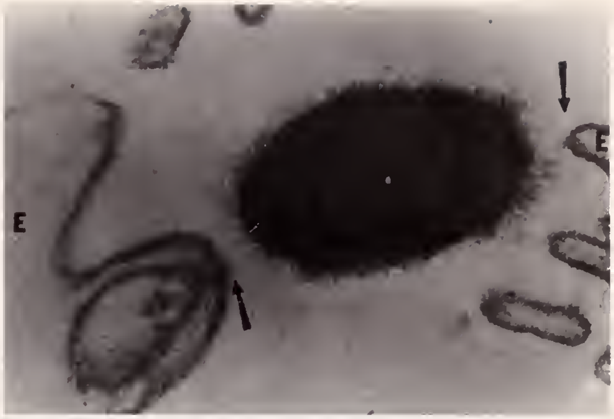

Fig. 3. Electronmicrophotograph of a group A streptococcus adhering to receptors on the surface of buccal mucosal cells (E) (Ref. 9).

Moreover, following the seminal studies of Charles Rammelkamp and his colleagues (14) at Warren Air Force Base in the late 1940s and early 1950s, our studies of mass prophylaxis with Bicillin at Great Lakes Naval Training Center (15) during my tenure at Northwestern University in Chicago showed how dramatically we could terminate raging epidemics of rheumatic fever in military populations. In this typical M19 outbreak (**Fig. 5**), only three patients developed acute rheumatic fever after mass prophylaxis was initiated. Ironically, the three patients were not given Bicillin because of a vague history of "penicillin allergy." Note, however, that all cases of streptococcal pharyngitis on this base were not eradicated from this population; the prevalent virulent M-type 19 strain disappeared, and with it, rheumatic fever.

A simplistic concept of rheumatic fever and group A streptococcal pharyngitis had emerged in the 1960s. Students learned that rheumatic fever was, in all of its features, a poststreptococcal infection. But it was already clear to me from my work and the work of others that not all group A streptococcal infection could cause rheumatic fever. The facts were that the epidemiology of group A infection had dramatically changed. Our studies at Children's Memorial Hospital, Chicago, with the late Alan Siegel and with Eloise Johnson (16) showed that GrAS infection of the throat that was mild and untreated did not result in rheumatic fever (17).

These studies aroused much controversy. Were these patients mostly "carriers"? If so, why did those in whom we demonstrated prospectively

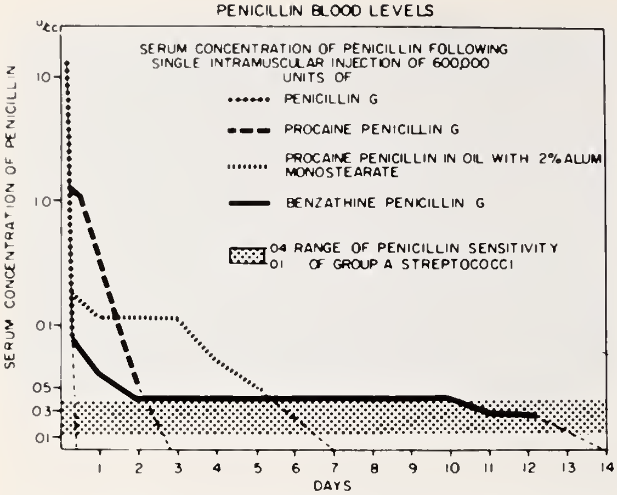

Fig. 4. Mean serum levels of penicillin in patients who received one I.M. injection of 600,000 U of aqueous penicillin G compared with single injections of three different repository penicillin salts (Ref. 11).

clear ASO rises not develop RF? Our numbers were considered too few for firm conclusions to be drawn and ethics committees frowned on further controlled studies.

Meanwhile, the virulent strains of streptococci that I called "rheumatogenic" were gone from U.S. populations. In the Third World's industrializing countries, however, rheumatic fever abounded (18). And with the disappearance of rheumatogenic strains from developed countries, along went rheumatic fever. Rheumatic fever declined spectacularly in Chicago in the 1970s (**Fig. 6**) within a period too brief to invoke genetic, economic, or any other socioeconomic changes in the Chicago population as a convincing explanation (19). Right up into the 1980s, studies of streptococcal sore throat in children showed the same frequency as always, but without any trace of rheumatic fever (20). Some of my infectious disease colleagues attributed this situation to good penicillin therapy, but few patients, if any, received benzathine penicillin G and few oral regimens ever commanded compliance with the 10 days of continuous treatment required to prevent primary attacks of rheumatic fever during epidemics caused by rheumatogenic GrAS. Even secondary rheumatic attacks disappeared, despite clear serologic evidence of intercurrent streptococcal infection in the patients with rheumatic heart disease that Alan Bisno and I followed in Memphis (21).

TABLE 2

Early Results in the Venereal Diseases Research Laboratory of the U.S. Public Health Service on Therapy of Syphilis with Two Forms of Penicillin

Stage	Drug	Dose × 10^6	% Relapse
1	PAM	1.2	12.8
	PAM	2.4	6.5
	PAM	4.8	2–5.0
	Benz	2.4	2–4.0
2	PAM	4.8	5.0
	Benz	2.4	4.0
3	PAM or Benz	6–9 (2–3 wks)	?

PAM, penicillin in aluminum monostearate; Benz, benzathine penicillin.

Rheumatogenic strains, I insisted, were gone. What are such strains? As the late Lewis Wannamaker and others had pointed out, they were not the GrAS that cause pyoderma. Our studies in Memphis with Alan Bisno confirmed that (22). By 1970, we clearly demonstrated the sharp separation of the epidemiology of poststreptococcal acute glomerulonephritis and acute rheumatic fever (**Fig. 7**). Moreover, during the hot months when rheumatic fever was gone, GrAS pharyngitis due to so-called "skin strains" was prevalent. In the Warren Air Force Base epidemics of rheumatic fever, several streptococcal M types were associated with the disease, each with the same rheumatic fever attack rate. From this observation grew the monolithic concept that rheumatic fever was not M-type dependent.

However, only a limited number of M types were demonstrated to cause rheumatic fever in that and other military populations. Moreover these strains were highly virulent, encapsulated variants which formed mucoid (hyaluronic-acid encapsulated) colonies. They were rich in M protein (**Fig. 8**). They were quite different from the pearly smooth strains isolated in sporadic cases of strep throat in civilian populations with no cases of RF. Such strains may still be M typable and may even belong to the common rheumatogenic M serotypes (23). When they dissociate and lose virulence, however, they lose rheumatogenicity Virulence can then be recovered, if at all, only by intensive mouse or perhaps human passage.

Most important, rheumatogenic strains have been shown by Edwin Beachey (24) and confirmed by Vincent Fischetti at the Rockefeller University (25) to have a greatly extended M protein molecule of repeating peptide units. This pep-M extract has been purified and the 14-unit peptide responsible for typability has been synthesized free of cross-reactivity with heart tissue. A multivalent vaccine for multiple rheumatogenic M types is potentially produceable, much as has

TABLE 3

Summary of Five-Year (1954–1959) Irvington House Study of Three Prophylactic Regimens to Prevent Recurrence of Rheumatic Fever

	Bicillin†	Oral Penicillin‡	Sulfadiazine§	Total
Patient Years	560	545	576	1,681
Strep infections (Rate per pt. yr.)				
Total	6.0	20.6	23.2	16.6
Confirmed*	4.3	18.5	17.7	13.5
Recurrences				
Number	2	30	16	48
Rate				
% per pt. yr.	0.4	5.5	2.8	2.9
% per strep infect.	5.9	25.5	11.6	16.5
% per confirmed* strep infect.	8.3	28.7	15.7	20.7

* Antibody rise.

† Benzathine penicillin 1.2 million units IM once monthly.

‡ 250,000 units daily.

§ 1.0 g daily.

been accomplished for the multivalent pneumococcal vaccine (**Fig. 9**).

Will we need a multivalent vaccine in the United States? The sudden outbreak of rheumatic fever in the mid-1980s in focal areas of the United States was startling. The outbreaks in military personnel at San Diego Naval Base and Fort Leonard Wood, Missouri (26), and those in civilian communities as far apart as Utah (27) and Pennsylvania occurred among middle-class school children who were getting usual medical care. At the most only a third of the latter had reported a previous sore throat severe enough to have made them seek medical treatment. Most intriguing has been the return of the famous rheumatogenic mucoid strains in these communities, especially M18, a notorious villain in World War II outbreaks in military populations.

The Fort Leonard Wood epidemic (**Fig. 10**) was terminated with benzathine penicillin mass prophylaxis and the M18 strain seems to have gone from that base. So has rheumatic fever, but not endemic streptococcal pharyngitis. In a recent report, a military health team bravely tried to

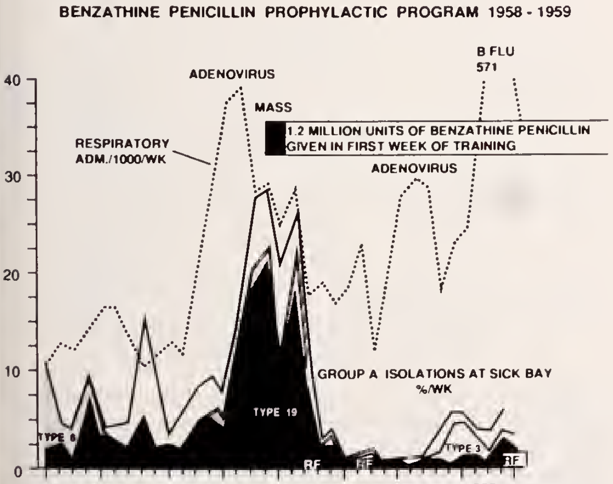

Fig. 5. Mass prophylaxis of rheumatic fever (RF) in a population of naval military recruits given 1.2 million U of benzathine penicillin G during an epidemic of type 19 group A streptococcal pharyngitis (Ref. 15).

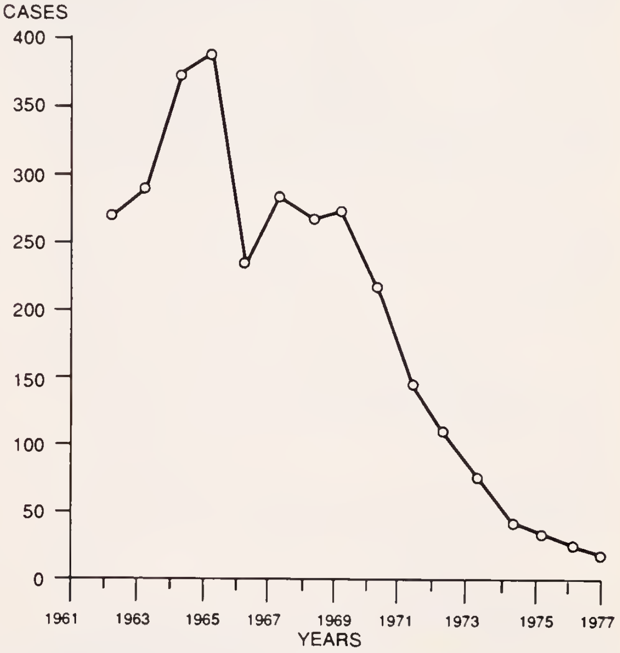

Fig. 6. Decline in number of patients with rheumatic fever or rheumatic heart disease registered annually in Chicago Board of Health's rheumatic fever registry between 1965 and 1977.

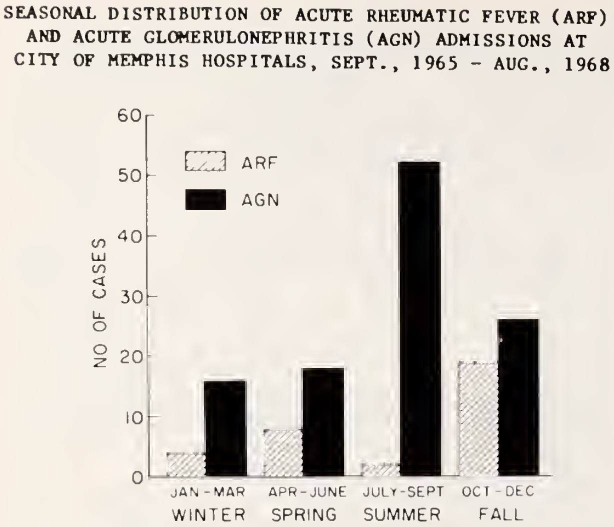

Fig. 7. Dissociation of epidemiology of acute rheumatic fever (ARF) and acute glomerulonephritis (AGN) in southern United States.

eradicate all cases of strep throat at one military base by vigorous use of benzathine penicillin therapy. They have also treated "penicillin hypersensitive" subjects with erythromycin. Rheumatic fever, however, disappeared from the base *before* these efforts were made. Why? Unfortunately, microbiological studies of the infecting pharyngeal strains on this base, including M-typing and colony morphology, were not made. Overzealous erythromycin treatment of GrAS sore throat, as in the 1970s in Japan (19), has caused the emergence of streptococci multiply-resistant to erythromycin, chloramphenicol, and tetracycline, but not to penicillin. The speed with which mutant strains emerge in a population under the selective pressure of antibiotics is awesome.

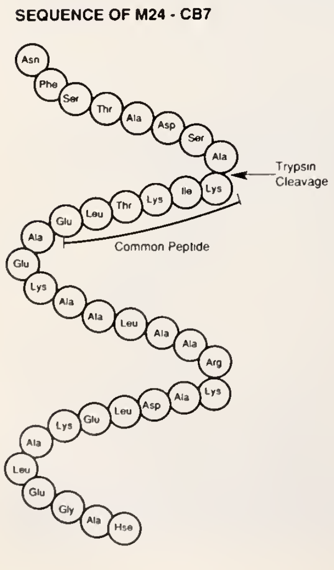

Fig. 9. Purification of M24 protein: Amino acid sequence of a small peptide containing the type-specific epitope (Ref. 24).

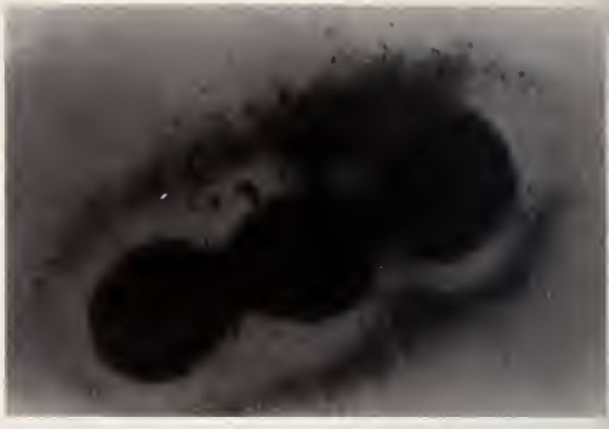

Fig. 8. Mucoid strain of rheumatogenic type M24 group A streptococcus grown in type-24 antiserum. Electronmicrophotograph showing precipitated Ag/Ab complexes around a large hyaluronate capsule.

Penicillin-Resistant Gram-Positive Organisms and Overzealous Cephalosporin Therapy. The selective pressure of intensive antibiotic usage is evident in the impact of the promiscuous use of third-generation cephalosporins, which is now becoming grimly apparent. Simplistic diagrams featured in drug-company-sponsored symposia show cephalosporins prepared to lick any kind of bacterium found in the human host (whether good or bad for your health). To our horror, the multiresistant strains of pneumococci, such as the one that arose out of the pneumonia-riddled pediatric hospitals of Durban, S. Africa, are slowly but surely finding their way around the world (28).

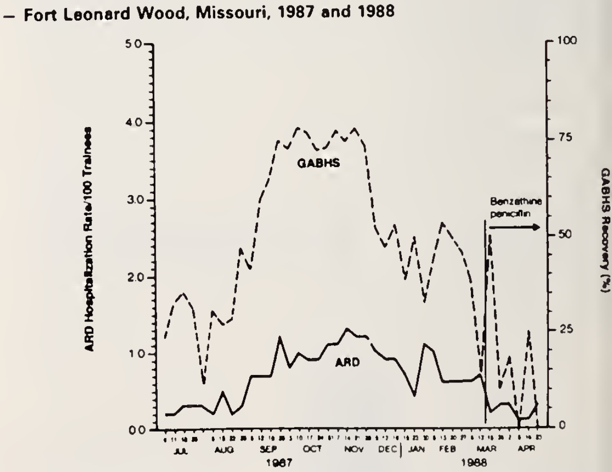

Fig. 10. Hospitalization for acute respiratory disease (ARD) (curve, left ordinates) and present recovery of group A streptococci (GABHS) (upper curve, right ordinates) among Army trainees at Fort Leonard Wood, Missouri, July 1987 to April 1988. Thirteen cases of acute rheumatic fever were diagnosed between October 1987 and February 1988. No new cases had been reported since the second week of March when benzathine penicillin G was given once to all nonallergic soldiers and thereafter to new trainees on arrival at the base.

As long as we continue to teach our students to treat pneumonia with shotgun therapy for community-acquired infections as though they were treating disease-compromised patients in the intensive care unit, pneumococcus mutants that can defy penicillin therapy will grow and prosper in the community. Sensible doses of penicillin should be used first when circumstances do not demand an urgent shotgun approach of broad-spectrum therapy.

Finally, I share with the British poet Hilaire Belloc these sentiments toward mine enemy who, unlike me, seems to grow no older, only more devious:

> He prayeth best who loveth best,
> All things both great and small.
> The streptococcus is the test,
> I love him least of all.

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Editorial

Did the Patient Tell Us?

With this issue the Journal *embarks on a new feature, a form of pathological-clinical correlation called here "Autopsy and Medical Care." The classical clinical-pathological conference is formatted to test the skill, expertise, and perspicacity of the discussant in choosing one or more differential diagnoses based on history, physical examination, and laboratory findings. The conference generally concludes with the findings presented by the pathologist and perhaps some additional remarks by the participants. Cases are usually selected to provide information of special interest with respect to the gamut of interesting if not unusual differential diagnoses.*

The approach in this feature will be somewhat different. Here, the findings by the pathologist have been given to the discussant. The task of the discussant is to reconstruct the patient's history and clinical course. With this format, the discussant is forced to focus on the meaning and significance of each or most of the pathologist's findings and how these might have influenced the patient's chief complaint, history, physical findings, and results of various special examinations and laboratory tests. In some ways, this format is analogous to the task in forensic medicine, where little or no prior information may be available other than the findings at autopsy. Readers are asked to conjure up their own fiction and test their imagination and creativity against that of the discussant. At the end of the hypothetical reconstruction, the patient's true clinical story is documented to permit a comparison of fact and supposition.

The objective of this exercise is twofold. Attention will have to be paid to all of the findings at autopsy, as well as how well the true clinical story and course, as recorded by the physicians caring for the patient, are reflected in these findings. It is hoped that this effort will hone the skills of taking and recording a history, sharpen insight into the relevance of such a history and the patient's clinical course, and enhance our profession's use of the findings at autopsy as an important objective assessment of the quality of care. This being the case, an effort to increase the autopsy rate must be made. Its present level as practiced in major medical centers is shameful.—SHERMAN KUPFER

Autopsy and Medical Care

Clinical Correlates of Pathologic Findings:

Case 1

Robert E. Siegel, M.D.

Autopsy: Clinical Information

- A 73-year-old black man with a 45 pack-year smoking history
- History of emphysema and gout
- Status post anterior resection for rectal adenocarcinoma in 1987; treated with postoperative radiotherapy
- Status post transurethral resection of his prostate for adenocarcinoma in 1989; treated with radiotherapy in 1990 and estrogen in 1991
- Last hospital admission 8/27/91; died 9/6/91

Autopsy: Pathological Diagnoses

Principal

I. Status post prostatic adenocarcinoma
  a. Extensive tumor emboli within pulmonary vessels
  b. Micrometastases, lung parenchyma and mediastinal lymph nodes
  c. Metastatic tumor nodule, liver
II. Status post resection with colostomy for rectal adenocarcinoma
  a. Multiple peritoneal adhesions

Secondary

- Acute bronchopneumonia, focal—left upper and lower lobe, right lower lobe
- Pulmonary emphysema, mild
- Arterio-arteriolo-nephrosclerosis, kidneys, mild
- Diverticulosis, colon

Autopsy: Gross Description

External. The body is that of a well-developed cachectic black male appearing the stated age of 73 years, measuring 6′1″ in length and weighing approximately 140 lbs. Lymph nodes are unremarkable. The breasts and nipples are normal.

Internal. The pleurae are unremarkable and contain 30 cc. of clear serous fluid. The pericardial sac transverse diameter is 15 cm and contains 100 cc of clear serous fluid. The diaphragms are at the 7th intercostal spaces anteriorly. The peritoneum is remarkable for multiple adhesions and contains a minimal amount of clear yellow-brown fluid. The liver edge is 2 cm below the costal margin at the right mid clavicular line.

Cardiovascular System. The heart weighs 490 g (normal 270–360 g). It has a normal configuration and the following measurements (normal values in parentheses):

Tricuspid valve 11.5 cm (10–12.5)
Pulmonary valve 9 cm (7–9)
Aortic valve 9 cm (6–7.5)
Mitral valve 10.5 cm (8–10.5)
Right ventricular thickness 0.5 cm (average 0.5)
Left ventricular thickness 1.5 cm (average 1.5)

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The myocardium is unremarkable and the aorta has mild atherosclerotic changes. The coronary arteries show patchy calcification and atherosclerotic changes with significant narrowing of lumens up to 75%. The superior and inferior vena cavae and portal veins are unremarkable.

Respiratory. There is no pneumothorax present. The right lung weighs 400 g (normal 360–570) and the left 360 g (normal 325–480). The pleural surfaces are unremarkable, with a moderate amount of anthracotic pigment. Except for mild emphysema, the parenchyma seems unremarkable. The trachea and bronchi appear normal and the pulmonary vessels are patent and unremarkable.

Hepatobiliary System. The liver weighs 1320 g (normal 1500–1800). The appearance is normal. There is a well-circumscribed yellowish-white firm tumor nodule measuring 1.9 cm in diameter 1 cm deep to capsular surface. The portal veins, hepatic artery, and portal areas are unremarkable.

Genitourinary System. The right kidney weighs 50 g and the left 170 g (normal 125–170 each). The capsules strip with difficulty revealing an irregular red-brown surface with fetal lobulations and no scars. The prostate is small, very firm, and yellowish-white in color.

All other systems were unremarkable.

Autopsy: Microscopic Examination

Lungs. Extensive tumor emboli were found within pulmonary vessels throughout all lobes of the lung bilaterally, occasionally obliterating vascular spaces. Some of these vessels have undergone reactive sclerosis and/or fibrosis due to complete embolic occlusions. Occasional micrometastases are found in lung parenchyma within alveolar spaces. Foci of acute bronchopneumonia with polymorphonuclear cell infiltrate within alveolar spaces are seen in sections of the left upper, left lower, and right lower lobes. Foci of bronchitis are also seen. Mild emphysematous changes are noted diffusely.

Mediastinal Lymph Nodes. Micrometastases with occasional giant cells are found in a mediastinal node.

Liver. A well-circumscribed metastatic tumor nodule with areas of necrosis is present within the liver parenchyma. The tumor is a moderately differentiated adenocarcinoma. Immunostaining for prostatic specific antigen and prostatic acid phosphatase is strongly positive. The remaining liver parenchymal architecture is intact with diffuse congestion and accumulation of bile pigment within occasional hepatocytes and canaliculi.

Heart. Multiple sections show moderately hypertrophied cardiac myocytes.

Kidneys. Scattered sclerosed glomeruli are seen in the kidneys bilaterally, more severely in the right. There is thyroidization of multiple tubules with accumulations of hyaline within tubular lumens. Diffusely thickened arterial walls with atherosclerotic changes are observed. There is a mild interstitial inflammatory cell infiltrate with mild congestion.

Prostate. Sections through the prostate reveal extensive fibrosis with no residual tumor present.

Large Intestine. Sections of colon show diverticulosis and no residual tumor.

All other organs were unremarkable.

Hypothetical Reconstruction of Clinical Case from Autopsy Findings

The following case history is reconstructed on the basis of the pathological findings delineated above. I have included expected laboratory and hemodynamic parameters and a probable clinical management of the patient. I discuss the pathophysiologic basis for the expected clinical findings. Finally, I discuss my reconstruction of the diagnostic studies, pathogenesis, and treatment of this patient's disease process with reference to significant clinical studies.

I would guess that a few years ago, the patient began to experience mild shortness of breath going up stairs as a result of his emphysema. Two to three weeks prior to this admission, I think he started to experience increased difficulty carrying packages due to dyspnea and the sensation of air hunger during basic activities of daily living, including bathing and shaving. His symptoms would have progressed until he felt breathless at rest, prompting him to seek the help of his physician and admission to the hospital. Episodic dyspnea progressing to dyspnea at rest is a common complaint of patients with tumor emboli or pulmonary hypertension.

Hypothetical Examination and Study Findings. On physical examination, he appeared cachectic. He would be in moderate respiratory distress, with a respiratory rate in the range of 25–30/min. His blood pressure might have been elevated to 160/90 mm Hg with a regular pulse rate of 120/min. The jugular veins would be distended with the patient sitting upright. The lungs would be clear on auscultation. Cardiac examination would reveal a loud P2 and an S3 which increased with inspiration. Abdominal examination revealed a 15-cm pulsatile liver without a palpable spleen. There would be no clubbing of the fingers or cyanosis but there would be 2+ edema of the lower extremities. Homan's sign was negative. A chest film would reveal borderline cardiac enlargement and clear lung fields. I would have a high degree of suspicion of pulmonary emboli given the clear lung fields, rapid onset of dyspnea, history of malignancy, and estrogen use.

The patient should have a high minute ventilation due to extensive emboli. Although the physical blockage of pulmonary arterioles and capillaries by tumor causes alveoli to be ventilated and not perfused, release of mediators and bronchospasm lead to hypoxemia. In addition, the plugging of capillaries with microscopic tumor emboli can cause a diffusion abnormality which can add to hypoxia. This patient should have all of the expected physical signs of pulmonary hypertension and right ventricular failure due to a significant reduction in the size of the functional pulmonary capillary bed. This is seen only with extensive pulmonary emboli, since the pulmonary vascular bed is a low-pressure, highly compliant circuit. Clinical appearance includes clear lungs, since the disease is confined to the vasculature and spreads to the lymphatics. If there is further spread to the bronchi, it is possible that one might hear a localized wheeze or feel a palpable rhonchus over a nearly obstructed bronchus.

In the emergency room, the results of an arterial blood gas test would have been pH7.48, pCO_2 26mm Hg, pO_2 48mm Hg and oxygen saturation of 84%. These findings would indicate respiratory alkalosis as a result of tumor emboli and metabolic acidosis secondary to lactic acid and hypoxia.

The patient would be anticoagulated with heparin for treatment of pulmonary emboli.

Other significant laboratory findings would include: hemoglobin of 10.4 g/dL, white blood cell count of 12,000/uL, alkaline phosphatase of 235 U/dL, SGOT of 145 U/L, SGPT of 200 U/L, lactic dehydrogenase of 250 U/L, and total bilirubin of 1.5 mg/dL. ECG was significant for a sinus tachycardia at 120 and a right bundle branch block (RBBB). Lung perfusion scan revealed multiple subsegmental peripheral perfusion defects. A pulmonary arteriogram was normal.

Heparin treatment was continued due to high clinical suspicion of pulmonary emboli, and broad-spectrum antibiotic therapy was begun to cover possible sepsis syndrome.

Elevated liver function tests reflect tumor emboli to liver and passive congestion from right ventricular failure. Tachycardia is secondary to increased oxygen consumption from increased work of breathing. Tachycardia is also the consequence of falling left ventricular stroke volume, resulting from decreased left ventricular preload due to right ventricular failure. High right ventricular pressure from pulmonary hypertension can cause decreased diastolic compliance of the left ventricle due to septal shift and reduced left ventricular stroke volume. The right bundle branch block is due to high right ventricular pressure effect on the superficial subendocardial right bundle of His. Pulmonary angiogram usually will not demonstrate emboli, since tumor emboli involve small arteries and arterioles, which are poorly evaluated by this test. A normal pulmonary angiogram would rule out significant thromboemboli, however, unless it is a technically poor study.

After thromboembolic disease was ruled out, the patient's clinical picture of tachycardia, leukocytosis, hypoxia, and abnormal results of liver function tests suggested sepsis syndrome. Although the chest film was normal, it was suspected that the patient's hypoxia was a result of early adult respiratory distress syndrome (ARDS) as a component of multiorgan failure. A diffuse alveolar filling process was expected to follow in subsequent films.

Hypothetical Clinical Course. The patient was transferred to the medical intensive care unit, where he deteriorated over the next 24–72 hours. Cardiac enzyme levels were normal and blood cultures were negative. Echocardiogram was performed to rule out tamponade as the cause of RV failure. Echocardiogram revealed a small pericardial effusion, tricuspid regurgitation, dilated right atrium and RV and good LV function.

As the patient developed worsening RV failure and hypoxia, a pulmonary artery (PA) catheter was inserted, so that hemodynamic parameters could be monitored and appropriate interventions made. Hemodynamic study revealed the following values: central venous pressure of 25 mm Hg (normal 2–8); pulmonary artery pressure of 62/36 mm Hg (normal systolic pressure 15–30 mm Hg; normal diastolic pressure 4–14 mm Hg); mean pulmonary pressure of 45 mm Hg (normal 8–18) and wedge pressure of 6 mm Hg (normal 2–12). The cardiac index was 1.8 $1/min/m^2$ (normal 2.4–3.8), and the systemic vascular resistance 2014 dyn · sec/cm^5 (normal 800–1500). Pulmonary vascular resistance was 962 dyn · sec/cm^5 (normal 100–300). High right-sided pressures and decreased cardiac output reflect right ventricular failure. Increased systemic vascular resistance is secondary to a hyperadrenergic state from falling cardiac index.

An increased serum lactate of 3.8 mEq/L (normal <2.0) reflected an inadequate oxygen uptake by the tissues. This patient had increased oxygen supply needs due to increased work of breathing. He also suffered from low oxygen delivery to tissues due to a combination of low cardiac index and low arterial oxygen content of blood (oxygen delivery = cardiac index × arterial oxygen content).

His respiratory status gradually deteriorated over the next few days. Despite a 100% oxygen mask, his respiratory rate increased to 40 per minute with hypoxia and he was intubated for impending respiratory failure. He was treated with volume loading and amrinone, with little improvement in pulmonary artery pressures or cardiac index. In light of a decrease in cardiac output from right ventricular failure, amrinone was the drug of choice for this patient. It is a myocardial inotrope and a vasodilator due to inhibition of phosphodiesterase activity. This agent is more effective at vasodilation of the pulmonary circuit then dobutamine, which vasodilates via β2 stimulation. When there was a failure of stroke volume to improve with amrinone, dobutamine was added, with some improvement in stroke volume. If amrinone is ineffective at increasing right ventricular function, dobutamine can be added, since it acts via a different mechanism, stimulating β receptors to increase ventricular function.

Bronchoalveolar lavage was performed to look for infectious agents and tumor. Neither *Pneumocystis carinii* nor malignant cells were found. Tumor emboli were considered likely in this patient, since hypoxemia without diffuse infiltrates would make the diagnosis of ARDS unlikely. Blood withdrawn from the distal tip of the pulmonary artery catheter in the wedged position was sent for cytologic examination and was reported positive for malignant cells. Cytologic examination of specimens obtained from either pulmonary artery capillary blood or from bronchoalveolar lavage can be useful in demonstrating invading cells. The patient developed increasing hypoxia with hypotension from right ventricular failure.

In light of the terminal state of the patient and diffuse metastatic disease, the family decided not to continue efforts to resuscitate this patient. The patient was sedated and was incapable of assisting the family with this decision. Ultimately he became bradycardic and developed electromechanical dissociation.

Discussion of Hypothetical Reconstruction

This patient died from microscopic pulmonary tumor emboli leading to pulmonary vascular hypertension, hypoxia, and right ventricular failure. The initial impression is usually that the patient has thrombotic pulmonary emboli, since there is a large overlap in the initial signs and symptoms of thrombotic and neoplastic pulmonary emboli. Patients with neoplastic pulmonary emboli have subacute dyspnea, cough, chest pain, and hemoptysis, in decreasing frequency (1). In a study by Kane et al., 8 of 16 patients with tumor emboli of pulmonary arteries and arterioles had severe, unexplained dyspnea (2). Initial signs include tachypnea, tachycardia, JVD reflecting high right-sided filling pressures, clear lungs, and a loud P2. Elevated liver function tests, reflecting metastatic disease, may help to differentiate this entity from thrombotic pulmonary emboli (2). A lung perfusion scan may reveal multiple peripheral defects or a "contour mapping" pattern, outlining bronchopulmonary segments. This pattern reflects small peripheral tumor emboli in patients with tumor microemboli and lymphangitic spread (3). This is different from the segmental and subsegmental defects seen in thromboemboli, which involve larger vessels. Pulmonary angiography is usually normal but may show slow filling, tortuosity, or pruning of small peripheral vessels (1).

Kane et al., in an autopsy review of 1085 cases of solid malignant neoplasms over a 15-year period, found an incidence of isolated microscopic tumor emboli, not associated with lymphangitic carcinomatosis, in 2.4%. The most common primary sites of tumor were prostate and breast, with liver involvement in 11 of 16 cases and liver the primary source of tumor in 3 of those 11 (2).

Metastatic tumor involvement of the lungs can have one of three distinct patterns or a combination of the three:

Microscopic Tumor Emboli. Tumor cells may be spread hematogenously to peripheral small arteries and arterioles, causing thrombus formation and sometimes fibrosis. This is most common with adenocarcinomas, especially of the breast or stomach, and is unusually common in hepatoma. It may occur in up to 10% of patients with primary lung carcinoma, and occurs more commonly in cancers with liver involvement (4). Patients initially have dyspnea, hypoxia, and clear chest films. This entity is difficult to differentiate from thrombotic pulmonary emboli. Patients may develop pulmonary hypertension and cor pulmonale or die from rapidly progressive right heart failure.

Lymphangitic Tumor Pattern. After hematogenous spread of tumor aggregates, intravascular tumor can spread through lymphatic channels into the interstitium, causing a lymphangitic pattern on chest film. Tumor may invade pulmonary parenchyma, causing nodules on chest film, or may invade bronchi to cause obstruction and collapse (5). Tumor may also spread medially via lymphatic channels to hilar and mediastinal lymph nodes. Neoplastic infiltration can cause peribronchial thickening and accentuation of interlobular septa. Patients usually have dyspnea. Chest films reveal increased interstitial markings, with or without nodules.

Pulmonary Artery Tumor Emboli and Infarction. Less commonly, tumor may lodge in segmental and larger arteries causing infarction, hemoptysis, and chest pain or sudden death (1, 6, 7).

Diagnosis of lymphangitic carcinomatosis can be made by bronchoalveolar lavage (8), transbroncheal biopsy of the lung (9), open lung biopsy or cytologic examination of capillary blood aspirated from a PA catheter wedged in a distal pulmonary artery (10, 11). It is unclear what the diagnostic yield of these procedures is in patients with clear chest films and microvascular emboli. In the cytologic study of blood aspirated from a wedged PA catheter by Masson (11), one of eight patients described had a clear chest film, and the diagnosis of metastatic prostate cancer was confirmed by both cytologic examination of pulmonary capillary blood and transbroncheal biopsy.

Autopsy. Autopsy of this patient revealed that the heart was enlarged, with a weight of 490 g (normal 270–360). The myocytes were moderately hypertrophied, yet right and left ventricular thicknesses were normal. The fact that the right ventricle was not appreciably thickened, despite widespread metastatic disease of the pulmonary vasculature, would imply that there was inadequate time for full right ventricular hypertrophy to accommodate increasing pulmonary artery pressures, thereby leading to acute right ventricular failure. Acute cor pulmonale is characterized by dilatation of the right ventricle. In chronic cor pulmonale there is also hypertrophy of the right ventricle in response to increased afterload. The most frequent cause of acute cor pulmonale is pulmonary emboli. Whereas the lung has significant thrombolytic potential and fibrinolytic activity can usually lyse showers of small and medium size emboli, tumor emboli occlude the vessels more permanently. The result is a dramatic increase in pulmonary artery pressures in response to reduction in vascular bed, humorally mediated vasospasm and bronchospasm with ventilation-perfusion abnormalities leading to hypoxic vasoconstriction. If pulmonary pressures rise rapidly, cardiac output begins to fall as mean pulmonary artery pressure approaches 30 mm Hg. Evidence indicates that the acutely loaded right ventricle fails as mean pulmonary artery pressure reaches the 40 mm Hg level (12).

Postmortem examination revealed an absence of residual tumor in the prostate, despite the fact that the patient died from metastatic prostate adenocarcinoma. This is not unexpected, because external radiation is effective in treating localized tumor (13). The patient most likely had stage C prostatic cancer (tumor with extracapsular extension) that had metastasized prior to treatment with radiation. Metastatic spread of cancer of the prostate is both lymphatic and hematogenous. Metastases occur most frequently to lymph nodes, followed by bones, lungs, bladder, and liver (14). However, lung and liver are uncommon as the sole metastatic sites.

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Actual Clinical Summary

The patient was a 73-year-old black man who was admitted to the hospital on August 27, 1991. One month before admission he began to notice dyspnea on exertion which gradually became worse until he was short of breath at rest. He developed a cough productive of small amounts of white sputum. There was no hemoptysis, chills, or fever. There was marked weight loss associated with anorexia.

In 1987, he had a low anterior resection with a permanent colostomy for adenocarcinoma of the rectum. He received pre- and post-operative radiotherapy, a total dose of 2000 rads. Two years later he had a transurethral prostatectomy, at which time cancer of the prostate was found. His treatment consisted of local irradiation and estrogen medication. In May 1991, a bone scan was done because of severe back pain. Multiple metastases were demonstrated in lumbar and thoracic vertebrae. Additional local radiotherapy to these areas resulted in amelioration of symptoms.

He had been a cook. He smoked one pack of cigarettes per day for 45 years, and drank only occasionally.

On admission there was evidence of cachexia and bitemporal wasting. He was tachypneic with a respiratory rate of 26/min. The blood pressure was 90/60 mm Hg, and the pulse rate was 120/min. His temperature was 98.8°F. The lungs were clear on auscultation.

On chest x-ray the lungs were hyperinflated with a paucity of markings. The diaphragms were flat. EKG revealed a normal axis with inverted T waves in leads II, III, and aVf. There was 0.5 mm depression of the S-T segments in leads V4–6.

Laboratory examination revealed a hemoglobin of 10.6 gm/dL and a hematocrit of 24%. The white blood cell count was 5,500/mm^3. The serum sodium was 136 mmol/L, potassium 4.0 mmol/L, chloride 101 mmol/L, and CO_2 content 16.4 mmol/L. The serum creatinine was 1.2 mg/dL, uric acid 9.7 mg/dL, alkaline phosphatase 653 U/L, γ-glutamyl transpeptidase (GGT) 165 U/L, aspartate aminotransferase (AST, SGOT) 79 U/L, alanine aminotransferase (ALT, SGPT) 93 U/L, and total bilirubin 1.1 mg/dL.

The arterial blood gases with the patient breathing room air were pH 7.50; pO_2, 42 mm Hg; pCO_2, 19 mm Hg; oxygen saturation, 84%; with the patient breathing 100% O_2, the arterial blood gases were pH 7.48; pO_2, 141 mm Hg; pCO_2, 22 mm Hg; oxygen saturation, 99%.

A VQ scan revealed heterogeneity of both lungs without discrete defects. The scan was interpreted as indicating low probability for pulmonary emboli. Repeat chest x-rays were unchanged, as were repeated blood gases. He received several transfusions and antibiotics. He was not heparinized. Two days before he died, diffuse rales and rhonchi were heard bilaterally. During the course of his brief hospitalization, he became progressively hypoxic despite supplemental oxygen and died on 9/7/91.

Narrative and Medicine

Oliver Sacks, M.D.

It's a special pleasure being here with you, especially the students among you, today. I never liked residents as much, but I loved students, who seemed much more unspoilt and open and less pressured and, in a creative way, less focused. In my teaching, the neurological rotation was eight weeks long. We had seven or eight students, and met them each Friday afternoon. In eight afternoons you can learn to know people pretty well. I loved that teaching, and I loved the students; I think they liked me. Sadly I've had much less to do with students since about 1974 because of changes in the medical school. Certainly one of the things I have been happy to preserve for 20 years is the Alpha Omega Alpha key which you gave me in 1970. It was a delight to meet you all informally this afternoon. I wish that meeting could have gone on for hours and hours, because I am actually much happier with dialogues than I am with lecturing, which is a monologue. I like dialogues. And I feel much more comfortable with a pen.

Being here today, then, has partly thrown me back on memories of being a medical student myself in London in the late 1950s and how it was then, at least how it was for me, how it was for some of us. I think we were probably somewhat less pressured than you: we didn't have so many exams, we didn't have grades, there wasn't so much competition. A lot of us were drunk most of the while. The medical student of that time has, I think, a somewhat different stereotype from the medical student now. For myself, I hated classes, I hated formal teaching, I didn't absorb any of it, but I felt very privileged at being free to go to patients and spend time with them. I've never been very good at learning from texts or lectures. My only texts have been individuals, have been patients.

In particular, I remember one patient who was an old tea planter from Ceylon in a terminal uremic delirium, who was babbling all day. His condition had been diagnosed as uremic encephalopathy. His utterances were delirious and therefore "nonsense" and "of no interest," and I was dissuaded from spending time with him. But I did spend time with him, I listened by the hour, by the day, and it was an amazing experience, like being privy to a dream. Gradually some of the landscapes of his thinking and his recollection became familiar to me, his symbolism became familiar to me. And then I started throwing in an occasional comment myself, and he responded to that, and this was like talking to a man in a dream and being both part of his dream and yet outside the dream. I think it was pleasing to him, because under the clutter of the delirium I think he felt very alone and very isolated, and knew that the end was close. So there was this strange relationship with a patient who was in a delirium, and for some reason it stays in my mind more than any other experience in medical school, and I feel it may have been a sort of prototype for what has happened since.

As medical students, we were, however, encouraged and made to tell stories and to give case presentations. And I loved also listening to the cases presented by my seniors. I hated lectures, I loved stories; I still hate lectures, I still love stories—which is why my so-called lecture may degenerate into a story. Medicine starts with stories. The patient has a story. He is a story. He tells you his story. It may not make much sense to him, but you help him to fill in the story, you make connections for him. You bring your own background, you bring your own cases, and gradually between you the story develops. As you

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heard earlier, I grew up in an atmosphere of medical stories. My mother, who was a surgeon, loved telling stories, which would sometimes start with a surgery or a tumor, or the pathology, but then spread out to the whole of life and would go on and on. Her style didn't differ whether she spoke to her colleagues, her patients or her students, the milkman or the gardener, or told stories over the dinner table. I think I partly derived from this my antagonism to the separation of the academic and the popular, and my feeling that a story well told should be accessible and transparent but should also have all the information one could want.

I got a little concerned listening to some of you earlier today and getting a feeling of a time of life where there might be no time, and much pressure and anxiety and urgency. But as I continued listening to you, it was also obvious that there were all sorts of deep and positive attachments. You would get interested, you would be delighted by things you heard. You would be drawn into caring for someone and into caring for phenomena. There is an obvious warmth and attachment in being a student of medicine, which perhaps one has more strongly than in any other studenthood. I was saying to some of you informally a bit earlier, and I want to say it again now, I think that graduation and residency may represent a sort of awful bottleneck and squeezing and constriction of life of a sort which you will never have to endure again. So I think you can have hopes that things will expand wonderfully later. Certainly this is what I found myself.

It did seem to me that as medical students in the lazy, drunken '50s, we had quite a lot of time before we failed our exams and got talked to very seriously. I think we often went to plays, and there were poetry readings, and there were concerts. My parents met as medical students at an Ibsen society for medical students. I think you need to make time for other things; I think this is terribly important.

Luria: Scientific Medicine and Narrative. I took my medical degree at the end of 1958. The following year, the Russian neuropsychologist A. R. Luria came to London and he gave some talks about the development of language, especially as he had observed it in some identical twins thirty years before. It was a wonderful talk in its intellectual depth and brilliance. (Also, this was the first time I had heard of Chomsky's work being brought into clinical discourse.) But it was also beautiful because his affection for these twins, whom he had seen thirty years before, shone through his words—one had the feeling of a man actuated by love. He was a grand analytic storyteller. When he talked in London, he told stories, but the stories were full of what he used to like to call "neuroanalysis," which is the neurologist's equivalent of psychoanalysis. I was very pleased that a man like Luria was alive and that I had a chance of listening to him, because I think already in the 1950s one felt the power of technology beginning to close in. There may also have been a certain hint that clinical medicine and clinical description were perhaps old hat, were obsolete, were being replaced by a more scientific medicine. But Luria himself embodied both scientific medicine *and* narrative, and these were brought together in his intense sense of history, of the unique development and becoming of each individual.

This was very different from the sense of constriction which I got from medical school, and I think it was partly to escape that sense of bottleneck that I bolted from England in 1960 and hitchhiked around Canada and the States and then went to California, where I thought everything was very loose—this seemed to me a good place perhaps to try and disorganize oneself in the hope that one might then re-organize oneself in a way that was more personal and more autonomous. As residents at UCLA, we had a journal club which met every week. There was a very big accent on the latest. I didn't like that; I wish there had been a history club. But I didn't very much like medical school or residency, as I've said, and it was a wonderful relief and surprise when I got out, and found the world was still there, and that there was a lovely sort of medicine which could stimulate and organize and allow one to develop oneself in a very personal way.

Migraine: The Whole Patient, the Complete Narrative. The first patients I saw when I got out of residency were patients with migraine. Migraine sounds dull: headache. But it's not just headache; it's a huge landscape. It's a wonderful subject, and it was the subject which first excited me neurologically, biologically. I had initially regarded my patients with migraine in purely neurological terms, but then I was called out of this attitude by patients telling stories and admitting me into their lives.

There were two patients in particular who changed my mind somewhat about things. One of them was a young man who got migraines every Sunday. These were severe, classical migraines, and it was a big event. The family would crowd around, and icepacks would be put on him, and there was a lot of sympathy. But strangely he had never really been given a specific medication for his attacks. So I stepped in and I said, "Let's give you some ergotamine," which is highly specific, as you know, or can be. The next Sunday I got a very excited phone call, saying, "It's wonderful. As soon as I had the aura, as soon as I saw the zigzag, I took the ergotamine, the headache didn't develop, and I feel great. You've changed my life." So that was nice. The next Sunday I didn't get a call, so I called him later. And in a rather dispirited voice, rather tired voice, he said he had had the aura, had taken the tablet, the migraine hadn't developed—but he said he had been sort of bored all day, he hadn't known what to do. His Sundays had always been richly filled with migraine; now he didn't know what to do, no one visited him. And he said he had a premonition, a foreboding, that something would happen.

The next Sunday I got an emergency phone call, not from him, but from his sister, saying he was in the throes of a status asthmaticus. He was very ill: he was on oxygen, and he was being given adrenaline, but later that day I talked to him. I then got a bit of history which I hadn't got the first time. He said he had had asthma attacks until he was seven, and then they stopped, and he had migraine attacks instead. And he added, "I want them back. I want my migraine back." He said, "I know where I am with the migraine." And he said something interesting. He said, "Do you think I *need* to be ill on Sundays?" This made me think in a way in which I had never thought before. I had simply thought in terms of the pathophysiology and the pharmacology of migraines, as a neurologist does think, but he had asked me a question in terms of needs, in terms of an entire pattern of a life. To abbreviate the story, I said, "Well, that's an odd suggestion, let's talk about it." And we talked about health and illness and the disposition of a life and whether he might need to be ill on Sundays and whether there was some alternative, some nonpathological alternative, to being ill on Sundays. And as we talked over a few weeks, his symptoms started to get less. I suppose this was some of my own discovery of the "talking cure" and of how essential it is to look at the whole patient and get a complete narrative and not just a particular symptom.

Case History: Pathography and Biography. When I was a resident I wrote several articles. They were articles with orthodox formats, and I had no difficulty publishing them. They didn't say much, they didn't provoke much. But when I started really to deal with patients, I had an irresistible need to tell their stories, and to tell at least what Hippocrates would call a pathography, a picture of disease, a story of disease, and sometimes to go on from there to a biography. As soon as I did that, I found that I could no longer be published in the medical literature. I think things have changed somewhat, but certainly in the 1960s it was very difficult to publish a full, individual case history. The notion was that science and clinical science should consist of lots of cases, and of an average, and the uniqueness of the individual rather disappeared.

As I had been very excited by listening to Luria in person when he came to London in 1959, so I was tremendously excited when in 1968 I read a book of his called *The Mind of a Mnemonist.* I started the book and read it for 30 pages thinking it was another one of those marvelous Russian novels, and then I realized it was a case history, a minutely detailed, densely detailed, systematic case history which somehow had the feel and the style and the sensibility of a novel. So Luria had done it again. He had somehow combined science with narrative into a form so right that one felt any other form would have been wrong. I was very excited and encouraged when I read this, and it gave me a feeling that I should write narratives, and publication be damned. But it's not easy to say publication be damned if you write things and they get rejected by medical journals. In a sense, I was forced by the situation to try to publish outside of medicine. So really my first expression of my experience with the *Awakenings* patients was not in *Neurology* or the *Archives of Neurology* but in a general journal in England called *The Listener*.

In 1972 Luria published another book, called *The Man with a Shattered World,* and I wrote a review of it which was published on the same day as *Awakenings* was. About two weeks afterward I got a letter, in fact I got two letters, from Moscow. The envelopes were addressed in a beautiful Victorian handwriting. Getting a letter from Luria excited me as much as getting a letter from Freud would have. In one of his letters Luria talked at length about the beautiful clinical narratives, the accurate clinical descriptions, of the last century, especially in neurology and psychiatry, and how these narratives collapsed or disappeared, or seemed to, with the rise of technology and statistics and physicalistic models of the organism, of the nervous system. He said, "The art of clinical description is almost lost now. It must be revived." I was haunted by those words. I still am haunted by them.

Artificial Language and Natural Language in Medicine. Let me jump back 300 years. When the Royal Society was founded in the 1660s, some guidelines were laid down for scientific writing. It was felt that elaboration, ornament, idiosyncrasy should be excised, that one should have writing that was transparent and without personality, and also writing of a universal sort, so that if it was translated into Latin or French or German the question of translation wouldn't matter.

The prescription for scientific writing laid down in the 1660s was not really a prescription for prose. I think it was almost a prescription for an artificial language. I think it is the use of artificial language which has become so repellent in medical writing today and sometimes makes it so opaque and so difficult of access. I don't know to what extent one needs a special language for physics and chemistry, but I don't think one needs a special language for medicine and for describing human predicaments which all of us know about, or all of us can imagine. I think that natural language is good enough for describing any human condition, any human condition whatever. And as physicians what we are concerned with is describing human conditions. I think that a good narrative, a case history, is not just idle deference to the past, I think it's not just an archaism, and it's not just being sentimental or dramatic.

Edelman and the Roots of Consciousness. This brings me as an ending point to what I think is one of the most exciting developments in neurology and psychology and biology and neuroscience at the moment. I'm not referring to all the wonderful new techniques of brain imaging and multi-unit recording and things like that, but rather to the theory of perception and perceptual categorization and learning and behavior and language and memory and consciousness which is being developed at Rockefeller University by Gerald Edelman.

Edelman got the Nobel Prize for his work in immunology and mechanisms in immune recognition, and he is now turning his enormous searchlight of a mind on what it means to be human and what it means to be conscious. What is emerging is something not at all like the computational model of the mind or the notion of thoughts as algorithms, but a view of the nervous system as always creative, as creating new categories of perception, of language, of consciousness—the notion of the nervous system as adventurous, as facing radical contingencies all the while and as coming up with new solutions.

The theory of development and of consciousness which comes out of Edelman's work is rather like a novel. It's full of richness and density and unexpectedness. When I started to read Edelman, I breathed an enormous sigh of relief, because it seems to me in a sense to vindicate and redeem the narrative and the case history by showing that the whole is supremely important, that nothing must be left out, and that every patient is unique and no two stories are the same.

I think in the 1990s we are going to see not only incredible advances in neurology and neuroscience, but a renaissance of clinical narrative. This depends, in part, on young doctors—on their reviving, in new terms, the ancient art of case history and clinical narrative. Good clinical narratives are as valuable as the "hardest" neuroscience, and indeed its natural complement. So I hope no graduating medical student will despise the clinical mode, but that each will become the creator of new narratives, of a new clinical sensibility and art.

Questions and Answers

Question: Did you like the movie [of *Awakenings*]?
Sacks: I thought the movie was interesting. I wasn't sure how a book, a thing made of language, would translate to a film. When I first saw the script I was absolutely bewildered—it consisted entirely of images and things like voice-over, which didn't convey anything to me. But by and large, although there are things that I think have been a little softened and sweetened here and there, I think the film does give an honest, tender picture of how things were in that summer of 1969. I think it has a feeling of respect for the patients and for the clinical process, and I do like it.

Question: Do you use technology?
Sacks: A certain amount, everything from a reflex hammer to evoked potentials. I have nothing against technology. I adore PET scans. I like SQUIDS, you know, both sorts, all sorts. Among some of my colleagues I sometimes see an identity crisis. Neurologists wonder if they are replaceable by a CAT scan. I think some of their diagnostic powers may be replaceable sooner or later by a PET scan, but I think their judgment isn't replaceable. No, I love technology. I want as much as possible, but I want it to be combined with the rest. And I like some words of Martin Buber: "We must humanize technology before it dehumanizes us." So I think we just must make technology part of human life, and richly.

Question: How did you feel at the end of the summer of 1969, when things started to fall apart?
Sacks: Frantic, anxious, bewildered, guilty. I first wondered if I was doing something wrong. Then after a while I was persuaded that it was not I who was doing something wrong, but that *things went wrong*. Why they went wrong exercised me for years and years, and when I started to read

about the theory of chaos in the late 1970s and the '80s, I suspected that it might be relevant. What I saw toward the end of the summer of '69, beyond the tragedies which were happening with the patients—well, in a way nothing is beyond tragedy—but in another realm what I saw was the unpredictable. And science is based on prediction. It was very threatening. It was epistemologically threatening to the patients, and to me, to all of us, to see the unpredictable. One of the things I like about some of the new theories, chaos theory and catastrophe theory, is they somehow make the unpredictable more understandable. And they bring new order out of chaos. But one of the things I actually had to do was to flee, which I did for three weeks, and to write, as I did then, the first nine case histories of *Awakenings*. So in some sense I went to narrative to try to digest the experience, to make sense of it, and to compose myself.

Question: Knowing the odds from your vantage point now, would you do the whole thing over again?

Sacks: Yes. I did hesitate for two years, despite the very optimistic reports from 1967. Our patients had an infinitely more complex disease, and they had been out of the world for decades. I didn't know what would happen. The spirit of doubt is stronger in me than the spirit of enthusiasm. I think the patients themselves at the deepest level had no regrets, except to say that they wished that L-dopa had been available ten or twenty years before, when they would have had less damage to their nervous systems, had lost less life, had to make less accommodation, and would have done better. I think that's the feeling.

Physicians Practicing Other Occupations, Especially Literature

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Abstract

Literature has been the favored nonmedical pursuit of physicians probably because the practice of medicine is suffused with narratives, the patient's history being one. Arthur Conan Doyle regarded medicine as a "grim romance," Somerset Maugham as an opportunity to see "life in the raw," and William Carlos Williams treated "the patient as a work of art." These sentiments may be linked to humanistic medicine. At some medical schools, literature is taught in the context of and integrated with medicine in an attempt to enhance ethics and empathy which were explicitly expressed by some physician-writers.

PHYSICIANS have made contributions to many fields other than medicine (1–4). St. Luke was a physician and so was the man who became Pope John XXI in 1276 (3). In Egypt 5000 years ago, the physician Imhotep was deified (3). Deification was not common, but Egyptians esteemed physicians. In a papyrus, the powerful hawk-headed sun-god Ra is contrasted with Sekhet the healer (5). For Ra, after creating life, abandons the living, whereas Sekhet lives among the sick, and he mends, he heals, he cares. Imhotep was also a scientist, engaged in architecture and astronomy (3).

Other physicians made magnificent contributions to sciences other than medicine (3), including Nicholas Copernicus (1473–1543), Carolus Linnaeus (1707–1778), Luigi Galvani (1737–1798), and Hermann von Helmholtz (1821–1894). William Wollaston (1766–1828) discovered palladium and rhodium, did research on the solar spectrum and on crystals, and invented the camera lucida. Peter Mark Roget (1779–1869) practice medicine for fifty years and not only wrote th *Thesaurus,* but invented a laboratory balance an a calculating machine (6, 7). Thomas Youn (1773–1829) did research on the eye (describin astigmatism, the mechanism of vision, a theory c color vision), revived the wave theory of light, o fered a theory of tides and elasticity, and, in a extraordinary display of deductive ability, mad the breakthrough in deciphering the Rosett stone which was completed three years later b Champollion (3). William Petty (1622–1687) cor structed the first catamaran, did the first scier tific surveying, served as professor of anatomy a Oxford, helped found the Royal Society, pioneere demographic analysis, and was the first econome trician (3); one display of his originality in ecc nomics is that he left a wealthy estate with clause in his will that his debts were not to b paid. The American physician Richard Gatlin (1818–1903) invented agricultural tools as well a the forerunner of the machine gun, which he o fered to the Union army, and it was accepted afte the Civil War ended (4).

Physicians became politicians, too, and c very different persuasions (8): Sun Yat Sen, th first President of the Chinese Republic in 1912 Georges Clemenceau, Prime Minister of Franc in 1917; François Duvalier of Haiti; Che Guevar of Cuba; Salvador Allende of Chile; and Howar

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Dean, the present governor of Vermont. Five of the 56 signers of the Declaration of Independence were physicians (8).

The physician who provided the most pervasive and beneficent effect on politics was John Locke (1632–1704). He practiced medicine much of his life (9, 10). At Oxford, where Locke was lecturer in Greek, in Rhetoric, and in Philosophy, Robert Boyle provoked his interest in science. He belonged to a group dedicated to reason and experiment, which included Boyle, Thomas Willis, and Richard Lower, a group that evolved into the Royal Society (9). In his medical practice, he collaborated with the great Thomas Sydenham. Locke's most memorable medical achievement (10) was to insert a six inch silver tube into his friend and patient, Lord Shaftesbury, to drain a hydatid abscess; Shaftesbury wore the tube the rest of his life. Locke's influence on political philosophy cannot be exaggerated. In his ringing proposal for the Constitution for Carolina, in 1669, he stated (10) that government rests on popular consent, that "All men are naturally in a state of freedom, also of equality," and that "No person whatsoever shall disturb, molest, or persecute another for his speculative opinions in religion or his way of worship."

It is believed (11) that some of the great Greek philosophers—Empedocles, Pythagoras, Democritus and Aristotle—studied medicine, as did the Persian philosophers Rhazes and Avicenna and the Spanish-Arabian Averroës. Albert Schweitzer (1875–1965) wrote *The Philosophy of Civilization,* as well as a biography of Bach and articles on Goethe, all the while managing medical care for the natives in Gabon, for which he received the Nobel Peace Price, and gaining fame as an organist. Other physicians contributed to music (1, 3, 12, 13). After Alexander Borodin (1833–1877) was graduated in medicine, he worked on a research project and for relaxation wrote *Prince Igor;* he also helped found a school of medicine for women. Leopold Damrosch (1832–1950) joined an orchestra soon after taking his medical degree, and as a conductor, introduced German opera at the Metropolitan Opera in New York City. Sam Wong, the new assistant conductor of the New York Philharmonic, is an ophthalmologist. Painting has not been neglected. Among contemporary physician-painters who have exhibited are Joseph Wilder, a surgeon at Mount Sinai Medical Center in New York; and Roy Calne, professor of surgery at Cambridge University, who does transplantations and conducts research on transplantation (14). Two other contemporary physicians became distinguished in yet other pursuits: Roger Bannister, the first to run the mile under four minutes, and Jonathan Miller, the director of plays and operas.

As a physician is needed on every ship, physicians were aboard to minister to pirates and buccaneers (15). Several rose to captain, one of whom discovered Alexander Selkirk, the original Robinson Crusoe, off the Chilean coast. Seagoing physicians varied greatly in their temperaments. At a time when cutting off ears for disobedience was common, one physician dressed the wounds of a prisoner despite emphatic objections by the captain. Not all were perceptive; one bought goat's dung believing it was ambergris. Because the chief surgeon was assigned to the flagship of the fleet, a pirate crew voted their physician to be chief surgeon in order to get rid of him. One physician was described as "a blustering braggadocio rascal, full of windy schemes." Another was sentenced to execution, but the sentence was never carried out because he had helped the authorities by betraying fellow prisoners, as he had earlier betrayed a fellow physician:

> A memory of roguery and laziness and knavery, you leave behind you, young Doctor Wilson. Your colleague Comry in the kindness of his heart fits you out with a clean shirt and drawers so that you may appear presentably before your pirate captain, you return his kindness by having him forced aboard against his will. You refuse to dress the wounded, and even your new pirate master tells you that you are a double rogue to be with him a second time and threatens to cut your ears off. All that saves your neck from the rope is betrayal of your fellow prisoners' plans for freedom. Better for your reputation you had stayed . . . at Cape Montzerado and rotted there of your nasty leprous indisposition (15).

They were men of their time and place, described

> as men not so different from their present-day colleagues, all kinds: the grave, the blustering, the whimsical, the tranquil; the pompous, the cantankerous; the cocksure, the lazy; the helpful, the kind; the roistering, the honest, and the knavish—all kinds but the picayune and the squeamish. Their surroundings may have fostered crime and sin, but no petty foibles; no paper rules and blanks to fill out, nor quarantines and surveys and public health regulations; only terrible foes, visible and invisible; terrible men, terrible disease, terrible tempests, heat, cold, hunger and thirst; terrible passion, greed, murder and savagery (15).

Many who became outstanding in other fields had begun to study medicine but abandoned it (3, 6, 11). Included in this group are the scientists Galileo, Humphrey Davy, Charles Darwin; the composer Louis-Hector Berlioz; the painters Jean-Frédéric Bazille and André Breton. Others who changed their course and became notable literary figures are Goethe, John Donne, Charles

Augustin Sainte-Beuve, Robert Southey, Samuel Coleridge, Henrik Ibsen, James Joyce, Gertrude Stein, Christopher Isherwood, and Georg Büchner. Büchner (16) died in 1837 at the age of 23, leaving behind three plays—each written in a few weeks—"Brechtian" plays, a hundred years before Brecht, which have greatly influenced modern theater. He had to flee Germany, abandoning medical studies, because of his political pamphlets urging human rights. In Zürich, where he taught and did research on comparative anatomy, he received a doctorate, but not in medicine (3, 6).

It is literature that has been the main other calling of physicians, the subject of reviews and compilations (1–3, 6, 7, 11, 12, 17–45). Biography was not ignored. Harvey Cushing's biography of William Osler won a Pulitzer prize (22). The French surgeon Henri Mondor wrote biographies of several French poets (26). But most of the work was fiction and poetry. It has often been pointed out that a linkage between medicine and the arts, including literature, is represented in mythology by Apollo, the god of poetry and god of the healing art, and his son, Asklepius, on whom the mantle of god of medicine fell. Theaters had inscribed special seats for the priest of Asklepios, and the theaters were located near the temples where Asklepios effected cures, not other temples (46). On the Acropolis in Athens, the theater and temple are connected by a ramp (46), and in Epidaurus, they face each other (46, 47). The propinquities have been suggested to be the reifications of the belief in the contiguity of art and medicine (47), or, at least, evidence that theater formed an integral part of the worship of Asklepios (46), offering "A healing word 'gainst many a foul disease / That all too long hath pierced with grievous pains" (46).

Metaphors and Eponyms

Figures of speech suggest associations, if not relations, between the arts and sciences, including medicine. Scientific principles and discoveries are common metaphors in the arts. Werner Heisenberg's uncertainty principle has been transmogrified to James Joyce's uncertainty principle (48). It took little time for the new science of chaos to become a consideration in literature (49). The genetic code has been made musical (50). Niels Bohr's complementarity principle is often invoked to argue that two paradoxical views are acceptable, even necessary. Metaphors and similes from poetry are less often used in science. An exhortation to biomedical scientists to learn quantum mechanics promised introduction "to an awesome achievement . . . at once abstract, esthetic, rigorous and real, like Marianne Moore's definition of a poem, 'an imaginary garden with real toads in it' " (51).

Some eponymous diseases and syndromes derive from literary characters (12). An advantage of an eponym is that it can embrace succinctly many manifestations of a disease that a more specific name may fail to include. For example, it has been pointed out that *Crohn's disease* (named after the physician who first described the disease) embraces pathology beyond the name *regional ileitis* (52). *Munchausen's syndrome,* from R. E. Raspe's stories of the unbelievable, fabulous adventures of Baron Münchhausen, is a patient's presentation of feigned symptoms and often fabricated signs of illness, convincing enough to lead to costly and successive hospitalizations, extensive tests, and invasive procedures that themselves produce morbidity (53, 54). The syndrome is common enough to consider in differential diagnosis (55). Munchausen's syndrome by proxy is the fabrication or induction of an illness in a child by a parent (56). From time to time, patients dismissed as having Munchausen's syndrome were later shown to have true disease, exemplified by Lyme disease (57). Unlike malingerers, these patients have no apparent objective for faking. Like the Baron, they travel widely, but their visits are to hospitals. The saga of a man with the syndrome was presented in verse (58):

He crashed through the door with a
  horrible racket,
Two hundred and sixty pounds at least,
And covered with blood like a wounded
  beast.
With gestures, he told us his chest was
  stricken—
The coughed-up blood made the residents
  quicken
To bring him assistance and ease his
  anguish.
Residents don't let "an emergency"
  languish.
Examined, his legs were red and swollen,
The large blue veins were easily rollen:
"Thrombophlebitis, then clot to the
  lung"—
The residents knew this, although they
  were young. . . .

His body was covered with many a scar,
He said from surgeons near and far.
The appendix went in County Cork,

A navel hernia in New York.
Once, he declared, in Portland, Maine,
A surgeon stripped out his saphenous
vein.
Surgical scars above one kidney
Came from an ectomy done in Sydney.
Another injury he wouldn't reveal us
Messed up his left internal malleolus. . . .

Munchausen's victims must be expected
To plague our lives unless deflected.
So be alert for this great nonesuchman—
Munchausen syndrome's flying
Dutchman.

Literary eponyms are sometimes strained or literally inaccurate. Baron Münchhausen's tales were obviously incredible and meant to amuse, whereas the lies of the patients are believable and meant to deceive (12). The *Raggedy Ann syndrome,* named after a character in children's books created by J. Gruell, is a condition of chronic lassitude, which does not describe the lively Ann but rather the flaccid doll that was made to publicize the book (12). The *Pickwickian syndrome,* extreme obesity associated with somnolence and hypoventilation, should be called the *Fat Boy Joe syndrome,* since Joe had it, not Pickwick, in Dickens' novel (12). Another eponym that distorts its literary root is the *Oedipus complex,* which only a convoluted extrapolation could relate to Sophocles' story of Oedipus Rex, who did not know until too late that the man he killed was his father or that the woman he married was his mother. Similarly, referring to exhibitionism as the *Lady Godiva syndrome* misrepresents the legendary Lady, whose body was hidden by her long hair in her gallop through Coventry, the purpose of which was not exhibitionism but to shock her husband into reducing taxes (12).

These literary eponyms are metaphors, which, John Locke insisted, are "wholly to be avoided" because "they insinuate wrong ideas" (59). Metaphors, like analogies, are dangerous if used in philosophy or in serious discussions of policy because they are extrapolations of one circumstance or thing to another that is intrinsically different. And they are dangerous if accepted as actualities rather than as figures of speech (60). Metaphors can offer vivid descriptions and stimulate useful associations. Medical literary eponyms, however unfaithful they may be to their literary sources, do not mislead, since all physicians agree on what they connote in clinical context.

Just as literature has enriched medical language, physicians have given their names to the English language. The verb *bowdlerize* comes from the physician Thomas Bowdler (1754–1825), who published expurgated versions of Shakespeare, the *Old Testament* and Gibbon's *History of the Decline and Fall of the Roman Empire,* expunging words and expressions that could not "with propriety be read aloud in a family" (3). It has been pointed out that if these omissions had not been made, young people would not have been permitted to read the books (3).

Very unbowdlerized is the work of another physician, François Rabelais (ca. 1494–1553), who gave us the word *rabelaisian,* derived from the bawdy, robust, scathing humor of his novels (61, 62). His *Gargantua* and *Pantagruel* are said to be drugs that would provide understanding and therapy (61, 62). He received a medical degree from Montpelier after becoming a priest. He moved to Lyons, where he taught anatomy, doing human dissections against church policy. Along with ribald novels he wrote medical articles and the first Latin translation of Hippocrates' aphorisms. His work embraced all that was known of Renaissance medicine (61). His fiction was condemned for mockery of religious practices, but he survived, probably because he was a friend of a cardinal, other churchmen, and politicians, and he was acquainted with the king. He is regarded as one of the greatest of all satirists and comic geniuses.

Physician-Writers and the Despotisms

Celine. Unlike Rabelais, some other physician-writers joined the despots or were despoiled by them. Louis-Ferdinand Céline (born Destouches) (1894–1961) practiced medicine almost all his life while writing, according to one critic, some of the greatest fiction in history (63). He was described as a kind and gentle physician, all the while writing novels that create a "garden of human disintegration" (64), searing and savage. Physicians are protagonists in some of the novels, which offer foul, gripping images of disease. He urged alliance with the Nazis and wrote violently anti-Semitic and racist pamphlets for them during the occupation. After the war, he fled to Germany, then to Denmark, where he was denounced as a collaborator in 1946 and imprisoned for 14 months (65, 66). The French condemned him in 1950 in absentia to a year in prison and a fine and declared him a "national disgrace" (65, 66). He was then given amnesty (66) and returned in 1951 to practice medicine and write. His house in Meudon, a Paris suburb, is being proposed as a listed historical monument by the French cultural ministry. Meudon provides a convergence of two physician-writers; 400 years earlier, Rabelais served as curate there shortly before he died (67).

Benn. Not well known in America is another physician-writer who was a Nazi for a short time, the German Gottfried Benn (1886–1956), who practiced both occupations almost to the end of his life (26, 68, 69). He wrote poems, plays, essays, short stories, and an oratorio that was set to music by Hindemith. As a medical student, he also studied philosophy and art while writing poems and short stories. He won a prize in 1911 from the University of Berlin for a study of epilepsy. His artistic goal was a synthesis of "scientifically exact description with modern expression" (68). The goal was attained early (1912) with the publication of *Morgue and Other Poems. Morgue* contains grisly descriptions of autopsies. The volume propelled him into fame. As a physician assigned to the German military government in Brussels in 1915, he participated in the trial of the English nurse Edith Cavell and signed the death certificate after she was shot as a spy. He practiced in Berlin from 1917 until 1935, specializing in dermatology and venereal diseases. His life (68) was chaotic and not benign. Soon after he was admitted to the poetry section of the Prussian Academy of Arts, Hitler came to power, in 1933. Heinrich Mann, president of the section, and Käthe Kollwitz, the artist, voiced opposition to the regime, warning of a relapse into barbarism. Benn replaced Mann as president, and did not protest the persecution of his Jewish colleagues. Rather, from 1933 to 1934, he supported the Nazis in essays and speeches, praising Hitler, demanding that intellectual freedom be sacrificed for the good of the state and for the future of the German people. Although his father and grandfather were Protestant ministers, he was denounced as a "pure-blooded Jew," and his certification as a physician was withdrawn. He had to prove his Aryan extraction. In 1934, he wrote a defense of modern art, which caused him again to be condemned, this time as a decadent cultural Bolshevist. He continued to avow loyalty to the Nazis until their crushing of an alleged plot changed his mind. He rejoined the army, which served as a refuge from Nazis, and wrote poems and essays to the end of 1944, criticizing the Nazi movement and both the Marxists and Nazis for extolling the collective rather than the individual. The Nazis prohibited his literary work from being published, as did the Allies during the occupation. In 1946, his attempt to publish the work he had accumulated since 1936 was blocked in Germany by Alfred Döblin, who in 1933 had been one of the ousted members of the poetry group. The Swiss published it in 1945, later the Germans. Benn's favorite biblical quotation, from Jeremiah, "God has walled me in, so that I cannot escape, and has laid heavy chains about me," is more appropriately applied to some of his contemporaries than to him. For him, the quotation has lost the pathos it may have had (if self-pity is granted pathos), as he was awarded numerous honors, including the Büchner prize, and he is now regarded as the most important German poet since Rainer Maria Rilke.

Döblin and Levi. Alfred Döblin (1878–1957), who temporarily thwarted the publication of Benn's later work, was a physician-writer. One of his somewhat expressionistic novels, *Alexanderplatz, Berlin,* stems from his experiences in a working class neighborhood (26, 70). A Jew, he left Berlin in 1933, came to America, and then settled in France after the war. He stopped medical practice after leaving Germany. His novels received much praise from Bertolt Brecht, not an easy achievement (70).

The Italian Jew Carlo Levi (1902–1975) did nothing medical with his degree, instead becoming an acclaimed painter and writer (26). Because he was an anti-Fascist leader, he was exiled in 1935 to Lucania in the south of Italy. His book *Christ Stopped at Eboli* is based on his experiences there. He also wrote essays.

Wolf. Friedrich Wolf (1888–1953), a Jewish physician-writer, studied medicine at Heidelberg while also studying sculpture and painting (71). He worked as a model for books on anatomy, displaying muscles that were well defined probably because he was active in track and field. He began to write stories and plays while serving as an Army doctor in World War I. He achieved fame as a dramatist in 1924, and for the rest of his life wrote plays, novels, stories, a libretto, movie and radio scripts, and Soviet propaganda. He stopped medical practice in 1933 when he fled Germany because of his political activities, eventually going to Paris. He had joined the Communist party in 1928, and worked and made speeches for the party. After the French released him from prison in 1940, he moved to Moscow, and in 1945 he settled in East Berlin. He was an East German diplomat to Poland and helped set the German-Polish border. His output was copious (71). His best-known work is the play *Professor Mamlock* (72), written in 1933 and produced in many countries besides Germany, including America. His son Markus was the leader of the very effective East German spy ring during the Cold War.

Bulgakov. A physician-writer who was almost destroyed by a totalitarian state was Mikhail Bulgakov (1891–1940), described as one of the greatest writers of the twentieth century (73, 74). He was graduated with distinction from Kiev University medical school in 1916, and four years later abandoned medicine to begin a career as a writer (73, 74). For the first year and a half of practice, without benefit of an internship, Bulgakov was assigned to provide medical care in a wilderness where wolves had to be kept at bay with a pistol on returns from night calls (75). The nine stories of his experiences there, real and imagined, have been collected (75).

One, *Morphine,* is presented as the diary of a physician who becomes dependent on morphine. It reads like numerous case histories, the horror and pity enhanced by Bulgakov's imagination. From the certitude that he will not become dependent, the physician declines inexorably to "surely mild habituation is not the same as becoming an addict?" then to injecting over 100 mg twice a day of "those life-giving crystals." Fear of exposure, the ruses used to get the drug, and the auditory and visual hallucination are presented: "At dusk—always my worst time—I clearly heard a voice in my room, monotonous and threatening, repeating my name. . . . It stopped as soon as I injected myself." And "the old woman was not running but actually flying, without touching the ground. This was bad enough; but what made me scream aloud was the fact that she was holding a pitchfork in both hands. . . . I fell on to one knee, holding out my hands to shield myself from the sight, then I turned and ran, stumbling, for home and safety, praying that my heart would not give out before I could reach my warm room . . . and take some morphine." All other interests are eroded. When asked by his mistress, "What can bring you back to life? Perhaps . . . that opera singer?" he answers, "I've got over her. . . . I have morphine instead." He tries cocaine:

> after giving my puncture-riddled thigh a careless smear of iodine, I dig the needle into the skin. Far from feeling any pain, I have a foretaste of the euphoria which will overtake me in a moment. And here it comes. I am aware of its onset, for . . . the faint, muffled snatches of music sound like angelic voices, and the harsh bass chords wheezing from the bellows ring out like a celestial choir. But now comes the moment when, by some mysterious law that is not to be found in any book on pharmacology, the cocaine inside me turns into something different. I know what it is: it is a mixture of my blood and the devil himself. The sound of . . . music falters . . . while the sunset growls restlessly and burns my entrails. This feeling comes over me several times in the course of the evening, until I realize that I have poisoned myself. My heart begins to beat so hard that I can feel it thumping when I put my hands to my temples. . . . Then my whole being sinks into the abyss. . . . I . . . who became addicted to morphine . . . warn anyone who may suffer the same fate not to attempt to replace morphine with cocaine. Cocaine is a most foul and insidious poison . . . today I am half dead.

Self-loathing increases and finally, suicide.

In 1928 Bulgakov had three plays running in Moscow, all of which were removed by censors whose objection to the content of the plays was exacerbated by their popularity (74). Of the 19 plays he wrote during his lifetime, eight were performed and 11 published in the Soviet Union (76). Maybe subscribing to Chekhov's belief that "great writers and artists should engage in politics only to the extent needed to defend themselves from politics," he wrote to Stalin in 1930, stating that 298 of the 300 reviews of his work were abusive and that the reviewers were *correct* in asserting that his work cannot exist in the USSR because "It is my duty as a writer to fight against censorship, whatever its forms and under whatever government it exists, and to call for freedom of the press. . . . I appeal to the humanity of the Soviet government, and beg that I, a writer who cannot be useful in his homeland, be magnanimously set free and allowed to leave" (73–76). Stalin answered Bulgakov by phone, refusing emigration but arranging employment at the Moscow Art Theatre, where Bulgakov served as literary consultant and assistant director. While dramatizing the work of others (*War and Peace, Don Quixote*) and writing librettos and movie scripts (74), he continued to write his own plays, novels, short stories, and a biography of Molière. The biography was not published, and a play about Molière, probably because of the enthusiastic response from the audience, was closed after seven performances on attack from *Pravda* (73, 77). The play depicted Molière's harassment near the end of his life by the sycophants surrounding Louis XIV, a circumstance, evident to everyone, that paralleled Bulgakov's treatment. In the sixties, some of Bulgakov's work was published, not surprisingly absent the novel *Heart of a Dog* (77). It is the story of a dog who is transformed by transplants into a repugnant, Engels-speaking man and becomes the government official assigned to purge the city of cats.

Bulgakov's work, like Chekhov's, showed hatred of oppression, and Bulgakov suffered for it. He was not corrupted or destroyed by the humiliations he endured—comparatively trivial ones like confiscation of his diaries and searches of his home—but he was ravaged by unremitting, vituperative opprobrium and vilification by the ideological zealots of a brutal political system. Bulgakov's torment by the Soviets is reminiscent of the treatment of Alexander Pushkin by the tsars, who censored his work, much of which still remains unpublished 150 years after his death.

Three years before dying, Bulgakov wrote to a friend, "Some well-wishers have chosen a rather odd manner of consoling me. I have heard again and again suspiciously unctuous voices assuring me, 'No matter, after your death everything will be published' " (74). The well-wishers were right. Not only are his works being published in Moscow as in the west, but the government gave him official honors on the hundredth year of his birth (78). His apartment in Moscow has become shrinelike, a place where people gather to read and discuss his works, covering the doors, walls and ceilings with tributes and graffiti, including "No to the Devil" (78), a reference to one of his great novels, *The Master and Margarita* (73), implicitly addressed in the novel to Bulgakov's government.

Some Medical Truants

Like Wolf, Döblin, Levi, and Bulgakov, many other physicians whose writings were successful abandoned medicine, joining the "medical truants" (1), defined as physicians who left medicine to become distinguished in other fields. Opposite odysseys were those of T. L. Beddoes, who left literature for medicine (18), and James Clark, who took up medicine after he failed as a writer, becoming Queen Victoria's physician (6).

Many literary critics would probably agree that among the truants, those who had the greatest effects on literature were Oliver Goldsmith (1730–1774), Friedrich von Schiller (1759–1805), John Keats (1795–1821), and Anton Chekhov (1860–1904).

Goldsmith. Goldsmith (6) began writing and selling ballads while a student at Trinity College in Dublin. He was generous. He impulsively gave his blankets to a poor family in Dublin and slept among the feathers of his bed to keep warm. When he went to take a boat in Cork, he met a woman with eight children and gave her all his money; his brother paid for his return to Dublin. His uncle gave him money to study law in London, which he gambled away before leaving Dublin. He studied medicine in Edinburgh, where Irish students rescued him from debt. He tried to practice medicine in London, and a friend reportedly advised him "to give up medicine on the grounds that if he were resolved to kill he should concentrate on his enemies." *The Vicar of Wakefield* and *She Stoops to Conquer* are considered classics, and he wrote poems as well, one of which, *The Deserted Village,* has been called "the sweetest poem in the English language" (11). He died, as he had lived, much loved and in debt. He was described by Oliver St. John Gogarty as "the gentle Irish Virgil."

Schiller and Keats. The German Schiller was forced by a duke to study medicine and to serve as an army surgeon before beginning his writings, which excited the wrath of the duke, compelling him to flee and to become, along with his friend Goethe, one of the founders of modern German literature (6). His *Ode to Joy,* used for the finale of Beethoven's Ninth Symphony, is one of his offerings. The Englishman Keats left the practice of medicine in 1806 at the age of 21 to write, in the remaining four years of his life, some of the greatest lyric poetry in the English language (21, 79–81). One encomium is that he is "the greatest of Shakespeare's successors" (18).

Chekhov. Chekhov certainly ranks among the greatest of physician-writers. Besides plays, he wrote short stories, novels, and volumes of letters. While studying medicine in Moscow on scholarship, he earned money to support his family by writing sketches. He received his degree in 1884. A monograph resulted from his three-month visit to the penal colony at Sakhalin, an island off Siberia, when he was 30 years old, after he had become known as a writer. In this, his only nonfiction work, he includes statistics on the island, based on interviews of all its inhabitants (82). Writing this took three years, and elicited his complaint of being "forced for the sake of a single mangy line or other to rummage among papers for a full hour" (82). He noted that one of the causes of death listed in records on the island was "lack of development towards life" (82), heralding the senseless diagnoses of dissidents made by some Soviet psychiatrists. After returning to Moscow, he arranged that thousands of books be sent to the schools on Sakhalin Island. One reason for visiting Sakhalin, he said in a letter (March 9, 1890), was, "I want to write one hundred to two hundred pages and thereby pay off some of my debt to medicine, toward which, as you know, I have behaved like a pig"; another reason that he gave after submission of the manuscript (January 2, 1894) was, "Medicine cannot now accuse me of infidelity: I have rendered just tribute to learning and to that which the old writers used to call pedantry" (83).

He sporadically practiced medicine, notably in 1892 when he worked to contain a cholera epidemic. His major commitment was to literature, as is clear from the progression of letters (83), some of them to Suvorin, a critic and—until Suvorin reviled the supporters of Dreyfus—a friend. One dated January 17, 1887: "Besides medicine, my wife, I have also literature—my mistress, but I do not mention her—those living in sin will perish sinfully." On February 11, 1893: "Medicine is my lawful wife, literature my illegitimate spouse. Of course, they interfere with each other, but not so much as to exclude each other." The wife did not triumph. On November 11, 1893: "I've become so devoted to it [literature] that I've begun to despise medicine." On January 21, 1895: "I am obliged to literature for the happiest days of my life and for what I am chiefly drawn to."

Chekhov wrote to a friend, "My Holy of Holies is the human body, health, intelligence, talent, inspiration, love and the most absolute freedom—freedom from violence and falsehood, in whatever form these may be expressed" (7). Health was the only one of the Holies he lacked. Tuberculosis and its hemorrhages assailed him most of his life, killing him as it had Keats. Despite a short life, his collected writings comprise 20 volumes. Maxim Gorky said, "In Chekhov's presence, everyone wished to be simple and truthful, to become himself" (7). He has been described as "a secular saint, the most attractive personality in the whole history of literature" (7).

Schnitzler. Arthur Schnitzler (1862–1931) practiced laryngology in Vienna, like his very accomplished father, while writing plays, poetry and novels (22). Physicians appear in one-third of his work. He dropped medicine before he turned forty to write full time. He is best known in America for *La Ronde,* a witty, clever play that was made into a movie by the French. The play was attacked as "pure smut" by the Society for the Suppression of Vice, and its staging in New York was prevented in 1923 (84).

His novel *The Road into the Open* has been described as a neglected masterpiece, "a book that the 20th century has misplaced" (84), and Schnitzler was described as "the doctor who left to literature his diagnosis of a society in crisis" (84). His work reflects his interest in psychiatry, causing Freud to describe him as his "double" and to write "Whenever I get deeply absorbed in your beautiful creations I invariably seem to find beneath their poetic surface the very presuppositions, interests and conclusions which I know to be my own" (84). After Hitler entered Vienna in 1938, the Burgtheater announced, "The day has come on which the stage of the Burgtheater is to be cleansed of the *Judenschmutz,* which was dumped there by Schnitzler and his consorts" (84). In 1941, at a celebration of Schnitzler's birthday ten years after his death, a Viennese emigré called Schnitzler one of "the voices that sound above the chaos, because their ring is so pure, because their prophecy is so true, because their humanity is so great" (84). Schnitzler's father had declared that "The religion of the doctor is humanity . . . the love of mankind" (84).

Some Irish, English, and Other Truants. Ireland has made an inordinate contribution to the list of physician-writers. One Irishman, Charles Lever (1806–1872), like his compatriot Goldsmith, composed ballads while at Trinity College, and he also sang them on the street for money. He gave up medicine in 1842, eleven years after receiving his medical degree. He wrote 30 novels in 35 years, becoming one of the most popular novelists of his time. One of his picaresque adventures occurred in Canada, where, after being admitted to an Indian tribe, he decided to resign. He was sentenced to death by tomahawk, but two Indians helped him to escape (6).

Somerset Maugham (1874–1965) embraced full-time literature right after his internship, writing novels, plays, short stories, and essays (85). His first novel, *Liza of Lambeth,* is based on his experiences in a London slum during medical training. *Of Human Bondage* is his novel about a medical student burdened by a clubfoot and, far worse, an obsession with as loathsome a woman as ever appeared in fiction. He was financially successful and the urbane sophisticate. Near the end of his long life, he became irrational. On a railway platform, a woman approached Maugham's companion to urge, "You should be gentle with this nice old man. He thinks he's Somerset Maugham" (6).

The British poet laureate Robert Bridges (1844–1930), who was also a playwright, gave up medicine at 40. A. J. Cronin (1896–1981) gave up a prosperous London practice to express his medical knowledge in best-selling novels. Similarly, Pio Baroja y Nessi (1879–1956) was a physician who became the most popular Spanish novelist of the 20th century (39). The French surgeon

Georges Duhamel (1884–1966) wrote novels and plays. One of the few American truants was the novelist Walker Percy (1916–1990), who gave up medicine when he became ill as an intern.

George Crabbe (1754–1832) failed as a surgeon and, though not a very successful poet, provided a description of physicians in verse (11):

> Men who suppress their feelings, but who feel
> The painful symptoms they delight to heal;
> Patient in all their trials they sustain
> The starts of passion, the reproach of pain,
> With hearts affected, but with looks serene;
> Intent they wait through all the solemn scene
> Glad if a hope should rise from nature's strife
> To aid their skill and save the lingering life.

Arthur Conan Doyle. Scots are a major group of physician-writers, comprising one-third in one compendium (6). Among them, or perhaps among all writers, no one wrote more popular fiction than Arthur Conan Doyle (1859–1930). His creation, Sherlock Holmes, has obscured other contributions of Doyle that have been recalled and praised (86–90). Doyle's grandfather emigrated from Ireland to Edinburgh and achieved fame as a caricaturist, as did one of Doyle's uncles, who did cartoons for *Punch,* designed its first cover, and did illustrations for Dickens and Thackeray (6). Doyle went to a Jesuit school and, at his mother's urging, studied medicine at the University of Edinburgh. Doyle's laments about his medical education (91) over a hundred years ago are echoed by students today, "one long dreary grind of . . . a whole list of compulsory subjects, many of which have a very indirect bearing upon the art of curing. The whole system of teaching, as I look back upon it, seems far too oblique and not nearly practical enough." And "I think that our educational tendency . . . was to expend undue attention upon rare diseases, and to take the common ones for granted. Many men who were quite at home with strange pathological lesions found themselves in practice without ever having seen a case of scarlatina or measles." A man of "Herculean proportions" (91), he excelled in many sports, including boxing (92). As a medical student, he spent seven months on an Arctic whaling vessel as a ship's surgeon. One of the crew with whom Doyle had boxed said Doyle is "the best surgeon we've had. He blacked my eye" (88). His prowess as a harpooner prompted an offer to double his salary if he would sail again (91). While doing well in his medical studies, he sold his fiction, and also worked as a physician's assistant to help support himself (88, 92).

After graduation in 1881, he served four months as a medical officer on a ship sailing to West African ports, and soon after returning, accepted a partnership in the practice of a friend from medical school, George Budd. Budd's practice was unusual. Each patient was given a ticket with a number designating his or her turn to see Budd; for a fee, the patient could move to the head of the line (88). Except for those patients in a hurry, consultations were free, and in return the patients agreed to pay for prescriptions that Budd dispensed and his wife bottled. The overflow of patients required a partner (91, 93). Budd became a character in Doyle's *The Last World,* which was made into a movie (91). Later, Doyle described his last meeting with Budd, quoting him: "I've taken to the eye, my boy. There's a fortune in the eye. A man grudges a half-crown to cure his chest or his throat, but he'd spend his last dollar over his eye There's money in ears, but the eye is a gold mine!" (93). Doyle left, but with no acrimony, for Budd provided Doyle one pound a week while he established his own practice (93). In a town healthier than its neighbors and one with a surfeit of physicians (90), Doyle's practice was moderately successful. During this period, in 1886, he wrote his first Sherlock Holmes story, the *Study in Scarlet* Rejected by three respected publishers, it was accepted by a house specializing in sensational literature that paid Doyle 25 pounds for rights that included the complete copyright, which eventually embraced movie rights (93).

Doyle became interested in ophthalmology and worked in an eye and ear infirmary. He went to Vienna for two months to learn ophthalmology and then opened a practice in London to do refractions and retinoscopy (88, 90). In eight weeks, no patients arrived. He spent his time writing and found a prominent literary agent. In 1892, he gave up practice to make a living as a full-time writer. His only subsequent medical experience was to serve four months as a physician in the Anglo-Boer War, for which he was knighted in 1902 (89, 93). The common belief that Doyle wrote fiction because he failed as a physician has been ascribed to the Bellman's fallacy, the repetition of statements from secondary sources without examining original, primary sources (12). It is certainly likely that even if Doyle's practice had been highly successful, he would have continued to write fiction, as he had been doing all his life.

The name Holmes was chosen because of Doyle's admiration for Oliver Wendell Holmes, about whom Doyle said, "Never have I so known and loved a man whom I had never seen. It was one of the ambitions of my lifetime to look upon his face" (93). He visited Holmes' grave in 1922–1923. While in New York, Doyle lived at 310 West 75th Street (94). The character Holmes was inspired partly by Doyle's study of the Edgar Allan Poe stories about C. Auguste Dupin, the amateur detective who worked solely by deduction. Holmes mostly evolved from Doyle's experiences with Joseph Bell, his teacher at medical school. Doyle wrote Bell in 1892, "It is most certainly to you that I owe Sherlock Holmes. . . . I do not think that his analytical work is in the least an exaggeration of some effects which I have seen you produce in the outpatient ward. Round the centre of deduction and inference and observation which I have heard you inculcate I have tried to build up a man who pushed the thing as far as it would go" (95). The resemblance between Holmes and Bell was so clear that Robert Louis Stevenson wrote Doyle from Samoa, asking, "Only one thing troubles me; can this be my old friend Joe Bell?" (96).

Joseph Bell descended from a family of prominent physicians in Edinburgh. Bell wrote two successful books on surgery, edited the *Edinburgh Medical Journal* for 23 years, and was revered by patients and students. He astonished everyone with his diagnostic acumen. Bell exhorted his students to "use your eyes, use your ears, use your brain, your bump of perception, and use your powers of deduction" (97). At the same time and independently, another great physician, William Osler, was urging his students to "Use your five senses. . . . Learn to see, learn to hear, learn to smell . . . for the whole art of medicine is in observation" (98). A successful diagnostician needs "an imagination capable of weaving a theory or piecing together a broken chain or unraveling a tangled clue" wrote Bell in a foreword to one of the Sherlock Holmes books (97). Parallels between statements by Holmes and by Bell have been collated (88, 97).

In developing Sherlock Holmes, Doyle wrote, "I thought of my old teacher, Joe Bell . . . of his eerie trick of spotting details." Revealing how Doyle emulated Bell and why Bell regarded Doyle as one of the best students he ever had and why he had selected Doyle to be his outpatient clerk is Bell's description of Doyle: "He was exceedingly interested in anything connected with diagnosis, and was never tired of trying to discover all those little details which one looks for" (95, 96). Asked to describe the details that provide salient diagnostic information, Bell offered an anecdote:

> A man walked into the room where I was instructing the students, and his case seemed to be a very simple one. I was talking about what was wrong with him. "Of course, gentlemen," I happened to say, "he has been a soldier in a Highland regiment, and probably a bandsman." I pointed out the swagger in his walk, suggestive of the piper; while his shortness told me that if he had been a soldier, it was probable as a bandsman. Well, the man . . . said he had never been in the army in his life. . . . Being absolutely certain I was right, and seeing that something was up, I did a pretty cool thing. I told two of the . . . dressers, to remove the man to a side room, and to detain him till I came. I went and had him stripped . . . under the left breast I instantly detected a little blue "D" branded on his skin. He was a deserter. That was how they used to mark them in the Crimean days, and later, although it is not permitted now. Of course, the reason of his evasion was at once clear (96).

Bell was not averse to telling anecdotes of his diagnostic gaffes: "You are a bandsman?" "Aye," replied the sick man. Dr. Bell cockily turned to his students, "You see, gentlemen, I am right. This man has a paralysis of his cheek muscles, the result of too much blowing at band instruments." And turning again to the patient, "What instrument do you play, my man?" "The big drum," came the reply (99).

Bell initially resented the publicity following Doyle's revelation of the inspiration for Holmes, writing to a friend, "Why bother yourself about the cataract of drivel for which Conan Doyle is responsible? I am sure that he never imagined such a heap of rubbish would fall on my devoted head in consequence of his stories" (99). Later, in addition to writing a foreword to one of the Holmes books, he sent Doyle suggestions for plots (97). Bell himself had a liking for criminal work; he collaborated with Henry Littlejohn, the police doctor in Edinburgh and later a professor of medical jurisprudence, solving major crimes (96).

Bell described a pervasive yield of the Holmes stories: "I believe they have inculcated in the general public a new source of interest. They make many a fellow . . . think that, after all, there may be much more in life if he keeps his eyes open. . . . There is a problem, a whole game of chess, in many a little street incident or trifling occurrence if one once learns the moves" (96). A century later it is independently stated that "education in the arts . . . provides an indispensable means of helping us develop our capacity to see. . . . The world's objects and situations, its everyday events, are replete with meaning waiting to be seen and heard by the watchful eye and the attentive ear" (100).

Sherlock Holmes became the greatest legendary figure of our time (90, 96), a mythic creature metamorphosed to a living person, provoking Sherlockitis, Sherlockidolatry [shortened to Sherlockolatry (101)], and in South America, the word Sherlock-holmitos, which is a pointless but impressive deduction (12). Holmes stimulates speculation of his true Baker Street address and the formation of hundreds of societies dedicated to him. The Baker Street Irregulars proclaim Watson as the true author of the Holmes stories, referred to as "The Sacred Writings," Doyle as his literary agent (102). Another suggestion is that Watson really solved the cases, but credited Holmes because of his innate modesty, his gentlemanly tendency to self-deprecation, and the fear of penalties that would be exacted on a physician who advertises (103). Publications abound about Holmes—the *Baker Street Journal, Baker Street Misc., The Sherlock Holmes Gazette,* and at least eight biographies. Holmes was awarded an honorary diploma from Colorado State University, and his picture appears on postage stamps (90). There are arguments about which university Holmes attended (6). A genealogy of Holmes concludes that "Nero Wolfe, purportedly a fictional creation of Rex Stout, was no doubt the illegitimate son" of Holmes (104). He has been the subject of over 300 movies, over 75 television shows, over 70 plays, over 30 radio series, the subject of musicals and ballet (90). Parodies of the Holmes story were written from the beginning. James Barrie, Doyle's friend and patient and author of *Peter Pan and Wendy,* wrote a parody to amuse Doyle (6). The physician Logan Clendening gave an account of Holmes' arrival in heaven, where Jehovah requests him to find the missing Adam and Eve, who had been major attractions there. Holmes succeeds. Jehovah wonders how Holmes so quickly identified them in a crowd, and Holmes replies, "Elementary, my dear God, they have no navels" (92). Rex Stout concluded that Watson was really a woman (102). William Gillette, the American actor, asked Doyle for permission to marry Holmes (102). One may anticipate the suggestion that Holmes predicted the Actors Studio method when he stated, "The best way of successfully acting a part is to be it" (97). And a prospective father may hope that a demand for equality of the sexes is not prophetic in the description of a woman who "insisted that her husband be handcuffed to her during her entire labor, which lasted eight hours. With the twisting during severe pains the iron had fairly eaten into the bone of the man's arm. She showed no remorse. 'He's got to take his share as well as me' " (89). On Robert Louis Stevenson, Holmes effected unusual cures, as Stevenson wrote Doyle from Samoa, struck by the "ingenious" adventures of Holmes: "That is the class of literature I like when I have the toothache. As a matter of fact, it was pleurisy I was enjoying when I took the volume up; and it will interest you as a medical man to know that the cure was for the moment effectual" (96).

Holmes' logic can be used to illustrate critical reasoning (105). His method of deduction is the same as that practiced by physicians in differential diagnosis (44), using erudition, rigor, and logic, precisely identifying all pertinent findings to diagnose the disease while eliminating others by precisely noting the absence of their signs and symptoms. A differential diagnosis was applied to the disease that Holmes feigned in order to catch a murderer in *The Adventures of the Dying Detective* (101). Holmes described it as a "coolie disease from Sumatra—a thing the Dutch know more about than we." The clever differential diagnosis (101) rules out metazoan, protozoan, spirochetal, and fungal infections, concluding it was tsutsugamishi disease, also called Sumatra mite fever and inundation fever, first described by the Japanese and encountered by the Dutch in Sumatra, where workers in rice paddies were bitten by the mites when the paddies overflowed.

Amusing diagnoses have been proposed to account for apparently contradictory statements by Dr. Watson about his war wound (106). In one Holmes story, Watson mentions having been struck by a bullet in the shoulder, and in a subsequent story, mentions that a bullet passed through his leg. One proffered explanation for the paradox is that the bullet in the shoulder caused, on occasion, diminished cerebral blood flow, leading Watson to forget the correct site of his injury. Another is that Watson was bending over a patient when hit in the shoulder with the bullet, which then ricocheted under the skin, traveling to his leg. A third explanation is that the bullet ricocheted after striking a bone in the shoulder, leaving the body to enter the leg. Other ingenious explanations to support a one-bullet theory have been offered. "Briefly, he was squatting over the edge of a precipice, of which there are many in Afghanistan, to answer the call of nature; and he was fired on from below. The bullet passed through the adductor muscles of the left thigh and struck him on his shoulder with the effects he has described. It has been objected that the account cannot be genuine because no marksman would take up by choice so hazardous a position, but this is surely to underrate the intrepidity and agility of the hardy Afghan mountaineer" (103).

Another conjecture is that, in fact, "the wound was located half way between" the shoulder and the leg, actually in the groin, but Watson could not mention it in deference to the sensibilities of the reigning queen, Victoria (107). Will an explanation be forthcoming based on Gödel's theorem of paradoxical undecidability?

Doyle wrote articles on medicine, but it is his fiction that is replete with references to medicine. In his non-Sherlock Holmes stories, over one hundred doctors appear (6, 86, 108). References to medicine in the Holmes stories have been tabulated, with note of the real patients he had encountered together with their fictional counterparts (89, 90). In the 60 Holmes adventures, there are 68 diseases, 32 medical terms, 38 physicians, 12 medical specialties, 22 drugs, six hospitals, three medical journals, and two medical schools (89, 90). They include descriptions of infectious diseases, cancer, gout, trauma, pulmonary disease, cardiovascular disease, ocular disease, geriatrics, insanity, and neurologic disease. The medical descriptions are sometimes vivid, like the man afflicted with gout who "could chalk his billiard cue with his knuckles" (89), presumably by extruding the tophaceous deposits.

Holmes has been claimed by several medical specialties, including rheumatology, dermatology, forensic pathology, ophthalmology, neurology (97, 109, 110); and it has been hinted that all the while he practiced semiotics, interpreting signs and symbols (111). Holmes is also regarded as a cognoscente of heredity, an interest stimulated in part by a close resemblance to his brother, who is described as even more misanthropic than he, a member of a club in which "no member is permitted to take the least notice of any other one" (112).

One can argue that pharmacology was Holmes' specialty, since 22 different drugs are mentioned in the stories (90), as well as 36 conditions due to drugs or toxins (97), including Holmes' use of cocaine. Watson's plea to Holmes to quit cocaine is pharmacologically sound: "Count the cost! Your brain may, as you say, be roused and excited, but it is a pathological and morbid process, . . . and may at last leave a permanent weakness. You know, too, what a black reaction comes upon you. Surely the game is hardly worth the candle. Why should you, for a mere passing pleasure, risk the loss of those great powers with which you have been endowed?" (88). Doyle himself was interested in drugs. He received second-class honors in Materia Medica and Therapeutics as a student (108). In a letter to the *British Medical Journal* while a medical student, Doyle described his self-experimentation with gelsemium (113), a plant containing the stimulant gelsemine. He wrote comments on the margins of his textbook of therapeutics, at least one of which, on opium, is correct: "I'll tell you a most serious fact / That opium dries a mucous tract / And constipates and causes thirst / And stimulates the heart at first" (88, 108). He also said, "Wondrous was the science which combined so many powerful drugs, and yet so accurately balanced them that they never modified the action of each other" (108, 114), a statement that would be revised today. Yet in an address to medical students in 1910, Doyle did not flatter therapeutics, likening its practice to a blind man's swinging a club at random, sometimes hitting the disease, sometimes the patient, the pharmacopoeia being the club (108, 114). However, almost all the drugs mentioned in the Holmes stories hit the signs and symptoms, though not the disease.

Since almost all the drugs affect the nervous system, if Holmes must be assigned a medical specialty, neurology can make the strongest claim. Moreover, the neurologic conditions mentioned in the Holmes stories have been collected (97, 109, 110): all four novels and 73% of the 56 short stories contain statements about a neurologic condition, totaling 104 examples. These obviously reflect the interest of Doyle, whose MD thesis was on tabes dorsalis (87).

Doyle's Non-Holmesian Interests. Besides Sherlock Holmes stories, Doyle wrote science fiction, short stories, including those on medical topics which have been collected (88, 108), historical romances, adventure stories, tales of boxing, poems, biography, newspaper reports about his visits to all fronts in World War I, a comic opera titled *Jane Annie* with James Barrie, and works on spiritualism (6). Doyle, irritated by the constant demands for more Sherlock Holmes stories, ended Holmes' life in 1893, only to feel compelled by readers to resuscitate him 10 years later. Doyle regarded the Holmes stories as "a lower stratum of literary achievement" (102). Doyle's statement, "if I had never touched Holmes, . . . my position in literature would at the present moment be a more commanding one" (89) may well be correct. His historical adventure, *Micah Clarke,* published two years after his first Holmes story, was praised by Oscar Wilde and other literary figures (6). Doyle's medical stories placed him "in the front rank of living writers," according to a review in a New York newspaper, and another American newspaper wrote, "No series of short stories in modern literature can approach them" (108).

Doyle's other accomplishments have been noted (6, 88, 91, 92, 108). Holmes' concern with mud, dust, stains, footprints, tobacco ash was new to crime-solving. The first report of identification of typewriting is due to Doyle. Before technical reports appeared on the subject, he commented on powder marks' defining the distance at which a gun was discharged (6). Alphonse Bertillon, who has been called the creator of forensic science, admitted his debt to Holmes and recommended his methods to police (6). Doyle's book about the Anglo-Boer War is regarded as a standard work (91). After visiting the fronts in 1918, he wrote a six-volume work on the British campaign in France. He was largely responsible for the British Navy's introduction of safety vests and collapsible floats (91). He was an early advocate of the Channel Tunnel. He founded a group to promote Anglo-American relations. He was president of the Divorce Law Reform Union. His pamphlets *The Crime of the Congo* helped force the Belgian government to reform the treatment of the natives (91), described by Doyle as "robbed, debouched, mutilated and murdered" (88); the pamphlets were published at his own expense, and profits went to the University of Edinburgh for a scholarship fund (92). His short paper describing the typhoid epidemic during the Boer War begins with a tribute to three groups who put in "more solid and unremitting toil than any others," and they were those who provided the food, those who worked on the railroad, and those who served as medical orderlies (115). He was revolted by cruelty to animals, while he castigated the "antihuman campaign" of the antivivisectionists, pointing out the many lives saved by inoculations developed in animals (88). He wrote letters to editors advocating vaccination against smallpox (88). He was nearly correct in his prediction in 1883 that "It is probable that in the days of our children's children, consumption, typhus, typhoid, cholera, malaria, scarlatina, diphtheria, measles, and a host of other diseases will have ceased to exist" (89). In 1890, after visiting Berlin to appraise the claim that Koch's tuberculin was a cure for tuberculosis, he questioned, iconoclastically and correctly, its efficacy (93, 108).

He wrote to *Lancet* and the *British Medical Journal* in 1907 requesting opinions from ophthalmologists about the imprisonment of a severely myopic man found guilty, on the basis of anonymous letters, of mutilating animals (116):

> Sir—Might I ask you in the cause of justice to permit me to put the following question to those of your readers who are engaged in eye practice? Do you consider it physically possible for Mr. George Edalji, whose degree of myopic astigmatism as determined by retinoscopy under homatropine is [the numbers are given] to have set forth without glasses on a pitch dark night with neither moon nor stars; to have crossed country for half a mile, climbing fences, finding gaps in hedges, and passing over a broad railway line; to have found and mutilated a pony which was loose in a large field, to have returned half a mile, and to have accomplished it all under thirty-five minutes, the limit of the possible time at his disposal?
>
> A consensus of scientific opinion upon this point would greatly aid me in getting justice for this young professional man, condemned for an offense which in my opinion he could not possibly have committed.

The man was freed. He attended Doyle's wedding (88, 108).

In 1910, Doyle told medical students what the medical profession offers (114): "that you are the friends of all, that all are better for your lives that your ends are noble and humane. That universal goodwill without, and that assurance o good work within, are advantages which cannot be measured by any terms of money. You are the heirs to a profession which has always had higher ideals than the dollar. Those who have gone before you have held its reputation high. Unselfishness, fearlessness, humanity, self-effacement professional honour—these are the proud qualities which medicine has ever demanded from her sons. They have lived up to them. It is for you youngsters to see that they shall not decline during the generation to come." A book was dedicated to Doyle "whose fundamental integrity ubiquitous optimism, boundless vigor, inherent compassion, animated humor, prescient imagination, and exceptional writing ability have given to future generations legacies in many genres not the least of which is humanistic medicine promulgated through fictional works" (108).

In his last piece of fiction, published in 1929 Doyle commented on the mores of the times "There was no longer . . . the cultivation of the mind, but we had a glimpse of a people who were restless and shallow, rushing from one pursuit to another, grasping at every pleasure, for even missing it" (91). A year later he died, spared having to witness yet further degeneration.

The epitaph on his tombstone reads "Stee True, Blade Straight" (92, 108).

Physician-Writers Who Continued Medical Practice

The list of physician-writers who did not become medical truants is also long and imposing Rufus Ephesius, physician to Cleopatra, wrote poems (11). The great Roman poet Virgil (70 BC–19 BC) was a physician (11). Girolamo Fracastoro (1483–1553) was a renowned physician, geologist astronomer, and poet, who named and described syphilis in a poem, *Syphilis or the French Disease* (12, 67), summarizing all that was known about the disease. Ambroise Paré (1510–1590) was surgeon to four kings and wrote sonnets (11). Thomas Lodge (1558–1625) took his medical degree when he was over 40, having been occupied as a lawyer, soldier, sailor and writer of plays, novels, pamphlets and poems (18). One of his works, *Rosalynde,* provided Shakespeare with the plot of *As You Like It*. He wrote *A Treatise on the Plague* in 1603 while the disease was raging in London, and died of the disease 22 years later (18). Thomas Campion (1567–1620) was physician, poet, composer and lutenist (11). Thomas Browne (1605–1681) made "the harmony between the physician and man of letters complete," revealing in "glowing and original expressions, the poetic sap which flows through all the minds of the age" (11). His *Religio Medici* "was written to reveal the soul in a physician" (11). Francesco Redi (1626–1698) disproved spontaneous generation and wrote sonnets (11). Samuel Garth (1661–1719) was considered the best poet of his time while engaging in political activities and serving as a physician to King George I, the Duke of Marlborough and other notables. John Arbuthnot (1667–1735) wrote the text for Handel's oratorio *Ester* while serving as Queen Anne's physician (6). He introduced John Bull in his writings. Arbuthnot was a Scotsman, as was Tobias Smollett (1721–1771), another physician-writer, whose novels influenced Dickens (6). Albrecht von Haller (1708–1777), whose ideas on tissue irritability provoked great activity by Galvani and others, was a poet and novelist too (11). Erasmas Darwin (1731–1802), the grandfather of Charles Darwin, practiced medicine and wrote a long poem on Linnaeus' botanical classification (6). René Laënnec (1781–1826) invented the stethoscope and wrote poetry (11).

Some Irish Nontruants. Ireland contributed to the roster of nontruants as well as the roster of truants (6, 7, 35). William Wilde (1815–1876) became a luminary of European medicine before the age of 40, honored by many universities. He founded the Dublin eye hospital, wrote a standard textbook on ear surgery and books on history, archeology, travel, fishing and other subjects. His wife was a poet and wrote articles ardently supporting Irish independence. After Wilde ended an affair, the ex-mistress accused him of seducing her under chloroform. Wilde's wife wrote a vitriolic letter to the woman's father, which engendered a libel suit. Although the award to the litigant was only titular because of her inconsistent testimony, Wilde never recovered from the scandal. His son Oscar's ending mimicked his (7).

Oliver St. John Gogarty (1878–1957) was graduated with honors from Trinity College in Dublin and also studied medicine in Oxford and Leiden. He practiced surgery all his life while becoming, according to W. B. Yeats, "one of the great lyric poets of our age" (6, 7, 35). He wrote prose and limericks too. Gogarty was one of the founders of the Sinn Fein, a senator of the Irish Free State, "the wildest wit in Ireland" (6), a master of repartee that was often acerbic, an aviator, a bicycle racer, and a champion swimmer. His athleticism was helpful. In 1923, he was kidnapped by armed men and escaped by diving into the river Liffey and swimming away under a hail of bullets. Earlier he received a medal for diving into the river to save a drowning man. By quick thinking, he saved the life of Michael Collins, one of the founders of the Irish Free State (6). He is now remembered mostly as James Joyce's drinking companion and the man portrayed as Buck Mulligan in Joyce's *Ulysses*. His comments on Joyce varied, sometimes disparaging (22), sometimes praising (35). He left Dublin for London, died in New York City, and was buried in Connemara. He was told he would not likely be praised as a poet until 50 years after his death (6). In the summer of 1992, Trinity College had an exhibition extolling its greats, and Gogarty received scant mention (117). We wait, comforted by the opinion that "there is no fear that his name will be writ in water" (18).

Oliver Wendell Holmes and William Carlos Williams. Two great American physician-writers practiced both occupations all their lives. Oliver Wendell Holmes (1809–1894), self-characterized as a member of the "Brahmin caste of New England" and admired by Arthur Conan Doyle, never left medicine and meantime wrote poems—many related to medicine—three novels, and numerous essays (118). William Osler considered him "the most successful combination which the world has ever seen of the physician and man of letters" (118). While briefly a law student, he relieved his boredom by writing poems, one of which, *Old Ironsides,* resulted in the preservation of *The Constitution,* a gallant ship that had been marked for destruction. He went to Paris to study medicine with Pierre Charles Alexandre Louis, who propounded the practice of scientific medicine. Holmes, adhering to Louis' principles, decided "not to take authority when I can have facts; not to guess when I can know." He received the M.D. degree from Harvard in 1836. A major contribution, in 1843, was *The Contagiousness of*

Puerperal Fever, a disease contracted during childbirth because, he charged, physicians and other participants failed to respect cleanliness. He recommended procedures to avoid infection. For making identical proposals, I. P. Semmelweis suffered ridicule, abuse, and banishment from Vienna and was driven to screaming on the street "Wash your hands!" before proving his hypothesis by dipping his cut fingers into an infected cadaver in Budapest, fatally infecting himself, and dying two months later in a mental hospital (65). On puerperal fever, as on all subjects, Holmes' rhetorical gifts were trenchant: "the time has come when the existence of *private pestilence* in the sphere of a single physician should be looked upon, not as a misfortune, but a crime," and "The woman about to become a mother . . . should be the object of trembling care and sympathy. . . . God forbid that any member of the profession to which she trusts her life . . . should hazard it negligently, unadvisedly, or selfishly." He became professor of anatomy and physiology at Harvard Medical School in 1847 and served for 35 years. He persisted in demanding a mindful practice of medicine, satirizing physicians who continued to practice archaic procedures like blood-letting in a poem titled *Rip Van Winkle, M.D.,* published in 1870. He was an effective and popular teacher, holding to a motto of "iteration and reiteration."

The greatest American poet among physicians, most would agree, is William Carlos Williams (119, 120), who during a long life (1883–1963) wrote essays, memoirs, stories, and the most original and influential American poetry of this century. For over 40 years he practiced in Rutherford, New Jersey.

Since about 1875 the list of physician-writers practicing both crafts is international. The Canadian W. H. Drummond (1854–1907) was dubbed "The Poet Laureate of British America" (18). Another Canadian, John McCrae (1872–1918), was killed in World War I (18), leaving us the poem *In Flanders Field.* The Czech Miroslaw Holub continued as a pathologist and writer (121). Tomio Tada, a professor of immunology at Tokyo University Medical School, recently wrote and had produced a Noh play based on a heart transplantation (122). Many physicians who achieved fame in the biomedical sciences wrote poetry and novels on the side; they include Edward Jenner, Charles Sherrington, Russell Brain, Henry Head, S. Weir Mitchell, and Wilder Penfield (18, 22).

Heightened Current Activity. In the past two decades, the number of active practicing physician-writers has increased remarkably. Much, though not all, of the writing stems directly from experiences in medicine. Among these physician-writers are Danny Abse, Howard Brody, Jonathan Cole, Bruce Dobkin, Colin Douglas, Henry Eisenberg, Robert Goldwyn, David Hilfiker, Perri Klass, Harold Klawans, Arthur Kleinman, Robert Marion, Russell Martin, Fitzhugh Mullan, Michael O'Reilly, Oliver Sacks, Kenneth Sanders, Léon Schwartzenberg, Richard Selzer, John Stone, Lewis Thomas, Gerald Weissman, and Irving Yalom.

Professional Groups and Publications. The heightened activity (27, 42) is manifest in the formation of the American Physician Poetry Association and The Physician Author Society, which publish a quarterly, *The Physician Author,* and offer workshops and seminars that provide credit for continuing medical education. *Literature and Medicine* is a scholarly journal published by the Johns Hopkins University Press, and a new one has been announced, *Mediphors,* described as a literary journal for the health professions. Physicians' penchant for writing poetry is evident in poems appearing weekly in the *Journal of the American Medical Association* and frequently in the *New England Journal of Medicine, Perspectives in Biology and Medicine,* and *The Pharos,* the journal of the medical honor society. The William Carlos Williams Poetry Contest for Medical Students is sponsored by the Northeastern Ohio Universities College of Medicine, and some of the poems submitted to this competition are published in the *Journal of the American Medical Association.*

Proposed Connections between Medicine and Literature

The plethora of physician-writers raises the question of the relation between literature and medicine or other sciences. The dual activities do not imply that medicine and literature have firm bonds, although many would hope so. William Wordsworth expected the sciences to become "proper objects of the Poet's art," also declaring "it is the passioned expression which is the countenance of all science" (123). Ezra Pound, perhaps influenced by his friend William Carlos Williams (119), is quoted as recommending that the proper method to study poetry is the method of contemporary biologists. John Dryden believed that a complete poet should be schooled in science (124), Matthew Arnold that science would be incomplete without poetry (19), and Robert Glynn that "a physician should be a kind of poet" (18). Samuel Coleridge hoped for communication between men in science and literature (124), anticipating a union of science and poetry (123).

It has been stated (125) that science and poetry, the "two great ways of seeing lie on the same imaginative continuum. They do not compete; they connect." A highly literate, highly gifted scientist (126) maintains that they do compete, they cannot be reconciled, and when one arrives, it expels the other. He believes that though "imagination is the energizing force of science as well as poetry" and though "they start in parallel . . . they diverge," because "in science imagination and a critical evaluation of its products are integrally combined," acting in synergy. Both poetry and science begin as stories, he asserts, but the stories differ in their purposes and in the kinds of evaluations of them. "All scientific theories must make sense . . . but in addition they are expected to conform to reality, to be empirically true." In this essay (126), science and literature are differentiated, and neither is derogated.

There is no yield in arguing whether or how closely literature and medicine are connected. Neither is harmed standing independently, and both are accessible. Chekhov, in answer to a letter (83) in which science was denigrated, demanded respect for both (May 15, 1889):

> You speak of the right of these or those kinds of knowledge to exist, whereas I speak not of a right but of peace. I want people not to see war where there is none. The different kinds of knowledge have always abided in peace with one another. Anatomy and *belles lettres* have an equally illustrious origin, the very same goals, the very same enemy—the devil—and they have absolutely nothing to wage war about. There is no struggle for existence among them. If a man knows the theory of the circulation of the blood he is rich; if, over and beyond that, he masters the history of religion and the lyric . . . he becomes not poorer but richer, ergo, what we are dealing with is only pluses. That is why geniuses have never waged war, and why, in the case of Goethe, the naturalist managed to live serenely side by side with the poet.

The view attributed to the genius playwright near-physician Büchner is that science and art simply represent "different perspectives from which to view the same subject" and "different languages with which to describe it" (16).

There is no question that the medical experience has influenced the literature of some physicians. Many have explicitly used medicine in their literature. In his obituary for Schnitzler, Thomas Mann wrote that Schnitzler's literary sensibility was "sharpened by the experience of a doctor" (84). Although assiduous searching is needed to find reference to medicine in Keats' poems, it has been concluded that "medical knowledge was . . . one of the fountains that flowed into . . . his poetic mind, bringing with it ideas and images" (80). Others praised the scientific method that medicine taught them. Chekhov wrote in a letter of November 1888 (83): "Those who have mastered the wisdom of the scientific method and are able to think scientifically experience many charming temptations. . . . Those who possess the scientific method feel with their souls that a musical composition and a tree have something in common, that both are created in accordance with equally regular and simple laws." On October 11, 1889, he wrote (83):

> I don't doubt that the study of the medical sciences seriously affected my literary work; they significantly enlarged the field of my observations, enriched me with knowledge, the true value of which for me as a writer can be understood only by one who is himself a physician; they also had a directive influence and probably because I was close to medicine I avoided many mistakes. Acquaintance with the natural sciences, with the scientific method, kept me always on guard and I tried, wherever possible, to bring my writings into harmony with scientific data, and where this was impossible, I preferred not to write at all. Let me observe that creativity in the arts does not always permit total agreement with scientific data; thus it is impossible to represent on the stage death from poisoning as it actually takes place. But agreement with scientific data must be felt in the conventions accepted, that is, it is necessary for the reader or spectator to grasp clearly that these are only conventions, and that he is dealing with an author who knows the true facts. I do not belong to the fiction writers who have a negative attitude toward science, nor am I one of those artists who think that they can arrive at everything by the intellect alone. I would not want to be one of them.

Arthur Conan Doyle gave similar testimony, telling medical students that medical education "tinges the whole philosophy of life and furnishes the whole basis of thought. The healthy skepticism which medical training induces, the desire to prove every fact, and only to reason from proved facts—these are the finest foundations for all thought" (89, 108, 114).

"Romantic Science" and the "Grim Romance of Medicine." If education in the scientific method were a major determinant of the association between writing fiction and an education in medicine, then a roster of novelists and poets would be rich in physicists and philosophers. The physician-writer association must have additional or other reasons. Pervading many (though not all) of the writings of physicians, as Oliver Sacks has noted (127), is what A. R. Luria described as *romantic science,* where the author presents "a patient . . . in his wholeness, while delineating simultaneously the intimate structure of his being," an "analytical description with a deeply personal empathetic feeling for the subjects" where "the syndrome . . . is embedded in a person. . . . And these are conjoined—the syndrome is always related to the person and the person to the syndrome—the personal and the scientific are always, hopefully, fused" (127).

In Doyle's speech to medical students in 1910 (89, 108, 114), he described medicine as a "grim romance," using *romance* to mean narratives that are marked by the emotional and imaginative appeal of human experience. It insufflates his writings and shows what is increasingly called "humanistic medicine." In his M.D. thesis on tabes dorsalis, Doyle wrote, "As the disease progresses the sufferer gets some relief from pain, the sudden shocks dying away and being replaced by analgesia. . . . Slowly the unfortunate victim sinks from one gradation of misery to another and can only look forward to the death which may reach him from pure exhaustion or may come from the involvement of the vital centres in the medulla." In recounting the influence of disease on history, he told the students that Napoleon's

> six years at St. Helena furnish a clinical study of gastric disease which was all explained in the historical post mortem, which disclosed cancer covering the whole wall of the stomach, and actually perforating it at the hepatic border. Napoleon's whole career was profoundly modified by his complaint. There have been many criticisms . . . of his petty, querulous and undignified attitude during his captivity; but if his critics knew what it was to digest their food with an organ which had hardly a square inch of healthy tissue upon it, they would perhaps take a more generous view of the conduct of Napoleon. . . . I think that his fortitude was never more shown than during those years—the best proof of which was, that his guardians had no notion how ill he was until within a few days of his actual death" (108).

In reply to a letter questioning the need for stark realism in his medical stories, Doyle wrote, "If you deal with this life at all . . . it is quite essential that you should paint the darker side, since it is that which is principally presented to the Surgeon or the Physician. He sees many beautiful things, it is true; fortitude and heroism, self-sacrifice and love, but they are all called forth (as our nobler qualities are always called forth) by bitter sorrow and trial. One cannot write of medical life and be merry over it" (108). Doyle presented one of the doctors' dilemmas experienced in his practice: "There was a grocer that developed epileptic fits, which meant butter and tea for us. Poor fellow, he could never have realized the mixed feelings with which I received the news of a fresh outbreak. . . . It was a ghoulish compact, by which a fit to him meant butter and bacon to me, while a spell of health for him sent me back to dry bread" (108).

Maugham too recorded the emotive effects of his experiences as a medical student (6):

> For here I was in contact with what I most wanted, life i the raw. In those three years I must have witnessed prett well every emotion of which man is capable. It appealed t my dramatic instinct. It excited the novelist in me. Eve now that forty years have passed I can remember certai people so exactly that I could draw a picture of them Phrases that I heard then still linger on my ears. I saw ho men died. I saw how they bore pain. I saw what hope looke like, fear and relief; I saw the dark lines that despair dre on a face; I saw courage and steadfastness. I saw faith shin in the eyes of those who trusted in what I could only thin was an illusion, and I saw the gallantry that made a ma greet the prognosis of death with an ironic joke because h was too proud to let those about him see the terror of hi soul. . . . I do not know a better training for a writer than t spend some years in the medical profession." He added in letter that same year: "I can only wish that I had remaine a doctor for three or four years instead of writing book which have long been dead as mutton (6).

William Carlos Williams had similar feeling after nearly 50 years of practicing medicine whil writing, mostly poetry (120): "as a writer I hav never felt that medicine interfered with me bu rather that it was my very food and drink, th very thing which made it possible for me to write Was I not interested in man? There the thing was right in front of me. I could touch it, smell it. I was myself, naked, just as it was, without a lie itself to me in its own terms." And "when th inarticulate patient struggles to lay himself bar for you . . . he reveals some secret twist of a whol community's pathetic way of thought . . . a man i suddenly seized again with a desire to speak o the underground stream which for a moment ha come up just under the surface . . . there is n better way to get an intimation of what is goin on in the world." And "the hunted news I get from some obscure patient's eye is not trivial. It is profound: whole academies of learning, whole ecclesiastical hierarchies are founded upon it."

Doyle extolled

> the value of kindliness and humanity as well as of knowledge. . . . A strong and kindly personality is as valuable a asset as actual learning in a medical man. I do not mea that trained urbanity which has been called "the bedsid manner," but the real natural benevolence which . . . cannot be simulated by any forced geniality. I have known me in the profession who were stuffed with accurate knowledg and yet were so cold in their bearing, and so unsympatheti in their attitude . . . that they left their half-frozen patient all the worse for their contact. While, on the other hand, have known . . . men who were of such exuberance of vitality and kindliness that . . . the mere clasp of their hand an light in their eyes have left their patient in a more cheer and hopeful mood (89, 108, 114).

These words are responses to suffering coupled with ideals. They voice the response to th patient not as a disease but as an ill person wit a disease entwined with a personal, emotiona life. Even if all—Luria, Doyle, Maugham

Williams, and the "secular saint" Chekhov—were explicitly taught this attitude in medical school, it is almost certain that not all their confreres became vested with the same feelings. All medical students at Edinburgh were urged by Joseph Bell, "Be kind and gentle" (99). Doyle, according to a classmate, was impressive "by his very kind and considerate manner towards the poor people who came to the out-patient department, whom I'm afraid some of us were in the habit of treating somewhat cavalierly" (90). In contrast, Doyle's schoolmate, George Budd, advised, "Break your patients in early, and keep them well to heel. Never make the fatal mistake of being polite to them" (91).

Very likely, each brought their feelings with them to medical school. Maybe the sensibilities of some writers allows them to experience empathic reactions as physicians. For "empathy has an esthetic component" (128). All were writers first; each was blessed with imagination. Doyle and Chekhov published while medical students. Maugham said that his only interest before medical school was art and literature (43). Williams wrote, "to treat the patient as a work of art made him somehow come alive to me. . . . The poem springs from the half spoken words of . . . patients" (119). Williams' son wrote (119) that his father sought a medical education for the income it would bring to pursue art, that medicine was secondary to poetry in his favor. Even while busy with medical practice, Williams wrote his mother that he had given up medicine for poetry; this statement—rhetorical, since he continued to practice—did not diminish his professionalism or his capacity for empathy. He wrote (119) of "adopting the patient's condition as one's own to be struggled with toward a solution. . . . I actually became *them* . . . so that when I detached myself from them . . . it was as though I were reawakening from a sleep." The empathetic feeling that medical schools would aspire to inculcate were seemingly intrinsic to their persons. Heroes cannot be imitated. But the sick would benefit if people with similar compassion and empathy could be selected for medical schools—if they could be confidently identified, and they cannot.

Pleas for a more humane, compassionate, empathic medicine have been made for centuries, including pleas by such great clinicians and teachers as Oliver Wendell Holmes, Osler, and Peabody (129). "To their patients what are the most scientific physicians if they know all things save the human heart?" (19). The ceaseless pleas clearly imply that the lack and the need are not new. In the past two decades, the entreaties appear like paroxysms of revelation and have grown to adjurements, presented by physicians and others (128, 130–133), often emotionally. We are ruefully asked if patients are seen as "human loaves of bread in the health-care supermarket?" (134). We are told, "We have priced compassion out of the American soul" (135). A hospital floor designed to treat a "patient like a person" and to "determine whether there is benefit to being nice to people" provokes the mock epiphany, "Caring. What a concept!" (136).

The increasingly vociferous outcry by physicians could suggest that medical practice has become less humanistic, rather than that patients have become more demanding. Maybe simple civility is under erasure, but other reasons have been proposed. Noncompassionate medicine has been attributed to increasing regulatory pressures that cause distractions from patient care, to a "craze for biomedical tests," and "to a reimbursement system that rewards costly technical procedures rather than clinical assessment" (133). For technical procedures, "we can bill the government . . . because they are easier to quantify than judgment, compassion and kindness" (134). A psychiatrist, deprived of reimbursable technology, has facetiously described experiments on a laser-based "psychoscope" that enables the ego, superego, and id to be separately visualized (137). In like fashion, another describes a PET scanner to examine fluctuations in Descartes' seat of the soul, the pineal body, a scanner that

> can be guaranteed to increase the earning capacity of American psychiatrists. . . . Because its immediate imaging properties make it ideal for office use, psychiatrists rather than radiologists can bill for it, and thus attain economic parity with other technology-based disciplines. Because it will no longer be necessary to inquire of the patient about the state of his or her soul, a notoriously time-consuming, uncertain and altogether messy procedure, time savings will be prodigious; productivity will increase; its cost-effectiveness will please both supply side and free market economists (132).

(Testing also provides data for defense against litigious assaults, as well as for diagnosis.)

Other reasons that have been offered for the apparent dwindling of compassion are that house officers and medical students are overworked and that too much science is taught in medical school. However, house officers have always been overworked, and they now have shorter hours than they had fifty years ago. Medical students have been overworked throughout modern times. Recalling his education over a hundred years ago, Doyle told students (89, 108, 114) that a medical curriculum

> sets a very high standard of strenuous work . . . it remains a precious heritage for life. To the man who has mastered Grey's [*sic*] Anatomy, life holds no further terrors. To remember that huge catalogue of attachments and ganglia and anastomoses is, I think, the most arduous task any of you will ever be called upon to do. But it is worth doing, for it leaves you with that ideal. In after life, when you are confronted with any task, you may say to yourself, "Well, I will do it as thoroughly and accurately as I did my anatomy at College" and if you do it in that spirit . . . nothing and nobody can stand against you. All work seems easy after the work of a medical education.

Attributing the ebbing of compassion to too much science in the medical curriculum is equally unconvincing. The bulk amount of science taught today in American medical schools is no greater than it was fifty years ago. It is the variety of science that has increased. Burgeoning sciences such as molecular biology are now appropriately included in the curriculum, but the time spent on these has been taken from other sciences; less time is given to gross anatomy, and students are not required to learn the anatomic details previously demanded. Moreover, at most American medical schools, the total scheduled teaching hours have fallen greatly over the past fifty years. One can argue that the students are, as always, burdened with too many facts while too little time is spent in teaching critical thinking—the ability to analyze data and to probe the validity of an inference. These and other changes in curriculum may well be indicated, but the technological advances in diagnosis and treatment rest on science. The teaching of science may need modification, but its abasement runs the risk of fostering ignorance, arresting the benefits that science brings, and, therefore, menacing patient care. It has been convincingly argued (133) that reducing the biological sciences will not teach physicians "to attend to the patient as well as to the disease." The objective is to "reconcile scientific understanding with human understanding" (130). What may be useful is additional science that relates to patient care—instruction in the social sciences (133) and effective instruction in the behavioral sciences (138).

Another suggestion is that recruiting students who majored in humanities to medical school will enhance humane medicine. Few would argue with Abraham Flexner's early proposal (139) that physicians should be educated in the humanities because descriptive skills and language could help to individualize patients. Humanities majors can add heterogeneity to a class, itself educative, and could make the class more interesting to teach. However, to presume that humanities majors are more humane is to traduce incoherently words of the same origin, rather like presuming that sociology majors are more social. Anyone working at a university would find difficulty in discerning a difference in the humanism displayed by a professor in the humanities and a professor in the sciences.

The humanities, especially literature, have been used in schools of medicine in the past twenty years, and more recently in law as well, in law to produce a new word, *poethics* (140). The purpose is not only to teach ethics, but, concomitantly, to increase the practice of humane medicine (38, 141–143). It has been emphasized that to be effective, the humanities should be taught in the context of medicine, integrated with medicine (144).

The "mere force of the imagination," David Hume wrote (60), could make a malady real and help students to experience, or at least to understand, the patient's feelings (130, 131, 145). The poet Percy Bysshe Shelley said, "A man, to be greatly good, must imagine intensely and comprehensively; he must put himself in the place of another and of many others; the pains and pleasures of his species must become his own. The great instrument of moral good is the imagination" (47). Even if Williams' habit of "adopting the patient's condition as one's own" were advisable, not everyone can do it. It is enough to understand the patient's feelings, to gain access to the feelings, maybe by recalling one's own feelings in an analogous situation or by imagining what one's feelings would be (145), a practice used by actors to understand a character in a script.

Carried further is the assertion that for imagination to provoke empathy, it must be linked to memory: "He who has never suffered is without empathy; it is as simple as that" (47). Samuel Johnson, in his biography of the great Dutch physician Hermann Boerhaave, asserted that Boerhaave's "own pain taught him to compassionate others" (33). An extreme of this view was offered by the French essayist Montaigne, who is quoted (146) as saying, "So Plato was right in saying that to become a true doctor, the candidate must have passed through all the illnesses that he wants to cure and all the accidents and circumstances that he is to diagnose. It is reasonable that he should catch the pox if he wants to know how to treat it." The goal of suffering may be ethically and readily achieved by admitting medical students in disguise to a hospital, a practice that has recently been instituted for house staff to increase sensitivity (147).

But literature as a teaching tool may be preferable to prescribed suffering. Literature, like the other arts, can evoke vicarious experiences by enlarging the imagination, show the uniqueness of people, and reveal importances by its ability to fabricate orderliness out of the obscuring randomness and chaos of living (29, 31, 141, 142, 148–150). Literature courses and reading lists are offered at some medical schools (30, 31, 141, 142, 151–153). In some courses, a literary expert, an ethicist, and a philosopher help the clinician to conduct the sessions (153). The readings are firmly related to clinical experiences (141, 152, 153). Selections are also made to show how sex, social class, cultural background, education, religion and race affect responses of patients and clinicians. A literature exists by women describing their health problems (154, 155). Literature that is devoid of political rhetoric is available about the mores, values, attitudes, and feelings of working-class people, as in James T. Farrell's *Studs Lonigan;* of blacks, as in Richard Wright's *Native Son,* the novels of Toni Morrison, and a recent collection of prose and poetry (156); of immigrants, as in Henry Roth's *Call It Sleep.* All could be enlightening to medical students, most of whom are still largely from the privileged class. They might learn that to some working-class patients, having a disease is to be a loser; that complaining about pain is not acceptable; and that some medical expressions are foreign to them: there is no diabetes in the family, but there is "sugar"; and he never had gonorrhea, but he did have the clap.

The visual arts (60, 161–164)—painting, caricatures—could also be useful in enhancing understanding and empathy. Holbein's painting *The Body of the Dead Christ in the Tomb* overwhelmed Dostoevsky. His wife recalls, "He stood for twenty minutes before the picture without moving. On his agitated face there was the frightened expression I often noticed . . . during the first moments of his epileptic fits. He had no fit . . . but he could never forget the sensation he had experienced . . . : the figure of Christ . . . whose body already showed signs of decomposition, haunted him" (165). At the least, the visual arts may be useful in enhancing the capacity to observe.

The Patient's History. The immediate relationship between medicine and literature, repeatedly pointed out, is that a patient's history and the progress of the illness constitute a narrative. It has even been subjected to the techniques of literary analysis (44). The initial history is "an inquiry," which, a historian writes, "is surely to require the telling of stories" (157). The stories require attentive listening; nearly half the patients in one survey believed that their physicians do not listen (158), maybe because most of them were raised on television rather than radio. Nevertheless, repeated studies have shown that the history alone, without the help of physical examination or laboratory studies, leads to the final diagnosis in more than half the patients (159)—not necessarily the half that are listened to.

Despite this success, some have decried that history-taking today has drifted from concern for the patient's thoughts and feelings. It has been suggested that physicians (and students) must stimulate the patient's narrative flow (145), which may, as Anatole Broyard wrote (160), help the patient enter the physician's heart. What may be especially revealing is a deeper anamnesis, to have a patient describe how he or she feels about a disease (130, 131)—how does a patient with cerebral palsy, or one who has been different in other ways since childhood, feel about having the infirmity and how it influenced his or her life?—a testimony providing a lesson in somatopsychiatry.

Oliver Sacks

Oliver Sacks is an accomplished practitioner of Luria's romantic science, of Doyle's romantic medicine. Oliver Sacks was described by Pauline Kael (166) in her review of "Awakenings," the movie based on his book:

> The neurologist Oliver Sacks is a supremely odd and complicated man. This bearded giant, a motorcyclist, a fern lover, and a weight lifter (who has been known to squat-press six hundred pounds), has a passionate curiosity about people. Born in London, in 1933, of physician parents who trained in neurology, and with two older brothers who became physicians, he grew up in a household where everybody swapped medical stories, and he has developed the clinical case study into an art form. Published as collections of essays, his narratives about his patients are speculative, exploratory, and maybe a little mad. He's drawn into his patients' aberrant states—he sees their abnormalities as brilliantly unique forms of consciousness to be charted—and, as he attempts to interpret them, he's drawn in further and further. He never closes off a subject; he goes on raising more possibilities, and his emotional essays sprout footnotes—excursions into ideas he's trying out. Reading him, you're absorbed in the play of his mind. (You may suspect that he is, too—that he's half bewildered by himself.) He probably makes more outré reaches of the imagination than any other essayist, and you might think you were reading freak-show detective stories if it weren't for the transforming power of his childlike sincerity and his tough-mindedness. Following him down a byway in a footnote, you think, This is loony, and then, as you read more of the tiny print, it doesn't seem so farfetched—it seems marvelously plausible. You entertain the idea, conscious that his interests are encyclopedic and he could go on footnoting forever. . . .
>
> A few months before the literary critic Anatole Broy-

> ard died last year, he wrote, "My ideal doctor . . . would resemble Oliver Sacks. . . . I can imagine Dr. Sacks *entering* my condition, looking around at it from the inside like a benevolent landlord with a tenant, trying to see how he could make the premises more livable for me. He would see the genius of my illness. He would mingle his daemon with mine; we would wrestle with my fate together."

Maybe the outstanding convergences of medicine and literature that Holmes, Doyle, Maugham, Luria, Williams, and others displayed are concisely put by Kael's "passionate curiosity" to be "drawn into . . . patients' aberrant states." Oliver Sacks is one who lives the convergences.

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Prevalence of Thyroid Autoantibodies in Ambulatory Elderly Women

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Abstract

Major improvements in thyroid autoantibody testing have now become widely available. Seventy-five elderly ambulatory women from a senior citizens' center (mean age 74.5 yrs) were studied to reassess the prevalence of thyroid autoantibodies and to demonstrate how such tests related to clinical signs and symptoms of thyroid disease. We used the enzyme-linked immunoassay (ELISA) technique for the measurement of autoantibodies to thyroglobulin (hTg) and thyroid peroxidase (hTPO) (as microsomal antigen), since ELISA systems are economical, highly sensitive and specific for population screening. Autoantibodies to hTPO (hTPO-Ab) were present in 44% and hTg autoantibodies (hTg-Ab) in 32% of the study group. Ten women (13.3%) had elevated thyrotropin (TSH) levels. An elevated serum TSH was associated with the presence of hTPO-Ab in varying concentrations. The mean TSH value of 7.2 μIU/mL in those women with hTPO-Ab was significantly higher than the mean of 4.7 μIU/mL found in those women without thyroid autoantibodies ($p < 0.01$). However, additional testing for hTg-Ab was of little clinical value.

These data indicate the high prevalence of thyroid autoimmune disease in the elderly female population. We conclude that screening for thyroid dysfunction is best achieved by the measurement of serum TSH in all women over the age of 60 years. The measurement of hTPO-Ab, but not hTg-Ab, was helpful in confirming the cause of thyroid failure in the elderly female population.

THYROID DISEASE in the elderly may present insidiously with nonspecific signs and symptoms erroneously attributed to the normal aging process or other medical conditions. This is particularly so for thyroid failure secondary to atrophic thyroiditis, where the absence of a goiter may mask the clinical diagnosis. Difficulty in the clinical diagnosis of mild thyroid failure has led to the suggestion that routine biochemical screening for thyroid disease in the elderly may be of value. An elevated thyrotropin (TSH) level remains the most sensitive indicator of thyroid deficiency (1, 2) and in various clinical studies, elevated TSH values have been found in 2.6% to 24% (3–5) of the elderly. Autoantibodies to human thyroid peroxidase (the microsomal antigen) (hTPO-Ab) and/or human thyroglobulin (hTg-Ab) autoantibodies have also been found in 7.4% to 42.2% of the elderly (2, 5–8). Unfortunately, these reports vary in patient characteristics, setting, and assay methodology, thus making it difficult to draw broad conclusions. However, most show a predominance of increased TSH levels and of hTPO-Ab and hTg-Ab in elderly women. The recent introduction of more sensitive techniques for the measurement of thyroid function and thyroid autoantibodies has caused such studies to require reevaluation, since it is now easier to apply them on a large scale. We have, therefore, performed a cross-sectional study of elderly, ambulatory women to determine the prevalence of abnormal thyroid function tests, including hTPO-Ab and hTg-Ab, by ELISA technology. This study has also allowed us to understand the relationship between such thyroid function tests and the

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signs and symptoms of thyroid disease in the elderly.

Methods

Patient Selection. Through an outreach program of the Department of Community Medicine, St. Vincent's Hospital and Medical Center of New York, volunteers were recruited at a senior citizens' center in the Chelsea neighborhood of New York City. There were approximately 1100 older people enrolled at the center, of whom 650 attended regularly, lived independently in the community, and traveled to the center for social contact. Three-quarters of the members were women. Seventy-five percent of the center members were white, 18%–20% Hispanic, and less than 5% black. All other ethnicities comprised less than 1%. The mean age of the center population was 74 years, with a range from 60 to 90 years. At the time of interview and examination, none of the participants were acutely ill, grossly malnourished, or taking any medications, other than thyroid replacement, known to interfere with the measurement of thyroid function.

Protocol. For a 15-month period, the opportunity for thyroid screening was offered to all center attendees through announcements at monthly meetings and a newsletter. After the purpose and protocol of the study were explained to the volunteers, informed consent was obtained. The subjects were evaluated using a questionnaire, physical examination, and laboratory studies which focused on data relevant to thyroid disease. The standard signs and symptoms of thyroid disease, as defined in general medical texts, were sought. Each participant was screened by one of two physician examiners who completed all aspects of the procedure in one session at the senior citizens' center. Appropriate follow-up was arranged for any abnormalities detected.

Assays. Laboratory studies included serum total T4, total T3, T3 resin uptake, thyrotropin (TSH), and thyroid peroxidase (hTPO) and thyroglobulin (hTg) autoantibodies (Ab). Specific immunoassays were used for T4 (T4-Tetra-Tab RIA by Nuclear Medical Labs), T3 (Abbott Labs), T3 resin uptake (Tri-Tab T3 Uptake by Nuclear Medical Labs), and TSH (Thyro-Shure by Nuclear Medical Labs) (normal range 0.5–6 μIU/mL). Thyroid peroxidase (as microsomal antigen) and thyroglobulin autoantibodies were measured by enzyme-linked immunosorbent assays (9) with results expressed in terms of an ELISA Index. Patients' results were obtained by dividing the absorbance of the unknown serum sample at a 1:100 dilution by the absorbance of a 10,000-fold dilution of appropriate standard. Background binding was removed from both data sets. Use of the index allows comparison between assays (9). The normal range for the ELISA indices, based on normal control population studies, was less than 0.2. We have found the ELISA technique to be 17% more sensitive than hemagglutination for assay of hTg-Ab and 12% more sensitive for hTPO-Ab (9).

Analysis. Data analysis was performed using the CLINFO statistical package of the Clinical Research Center at the Mount Sinai School of Medicine. The functions utilized included the Fisher exact test, chi-square analysis, and Student's *t*-test with a pre-set significant *P* value of <0.05.

Results

Demographics and Symptoms and Signs. The first 75 women volunteers aged 61–87 years were surveyed. Their mean age was 74.5 years. Ninety-two percent were white, 5.3% Hispanic, 1.3% black, and 1.3% native American. Twenty-three of the 75 (31%) had a known history of thyroid disease. In the review of systems, the prevalence of certain nonspecific symptoms of hypothyroidism was: memory loss, 50 subjects (67%); weakness, fatigue, or lethargy, 27 (36%); depression, 22 (29%); constipation, 17 (23%). Bradycardia was not detected. A goiter was present in 13 participants (17%), three of whom had abnormal TSH values (see below), and another four of whom had a history of thyroid replacement therapy more than 10 years earlier. Clinical signs of overt hypothyroidism were found in only one subject (1.3%).

Thyroid Function Tests. The mean T4, T3, and T3 resin uptake were 8.8 μg/dL, 117.7 mg/dL, and 37.5 respectively. The median TSH value was 4.5 μIU/mL; the mean TSH value of 5.8 μIU/mL was skewed to the right by the presence of three high values (see the **Fig.**). Only one woman (1.3%) in the study had an abnormally low T4 value. This participant had no known history of thyroid disease, but was clinically hypothyroid, with a markedly increased TSH. Ten of 75 participants (13.3%) had an elevated TSH defined as greater than 7 μIU/mL (two standard deviations above the laboratory mean) (**Table 1**). Three of these 10 women had a history of thyroid disease but were not receiving treatment; seven were newly diagnosed. There was no significant association found between an increased TSH level and patient demographics, signs and symptoms of thyroid disease, or T4, T3, and T3 resin uptake values (Table 1).

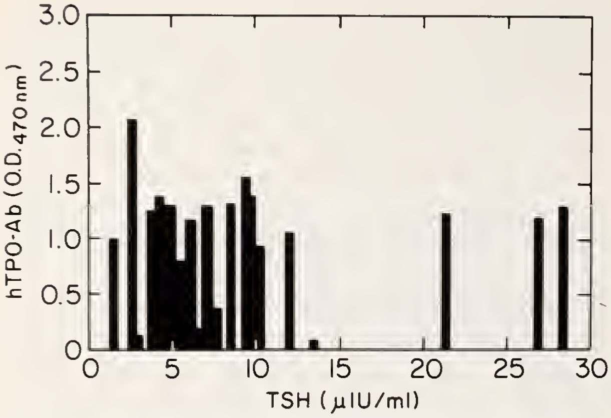

Fig. Comparison between serum TSH levels (μIU/mL) and the level of hTPO-Ab measured as ELISA absorbance.

Thyroid Autoantibodies. Autoantibodies to hTPO were present in 33 of the 75 women (44%), and to hTg-Ab in 24 subjects (32%) (**Table 2**). Both autoantibodies were found in 21 subjects (28%), and 36 subjects (48%) had one or both autoantibodies present. There was a direct correlation between the level of hTPO-Ab and the level of hTg-Ab; those with high titers of one antibody tended to have high titers of the other ($r = 0.633$, $p = 0.001$). Of the 13 participants with a goiter, 8 (62%) had hTPO-Ab present, and 6 (45%) had hTg-Ab present. None of those with a goiter had hTg-Ab without hTPO-Ab.

Nine of the 10 subjects (90%) with TSH values greater than 7 μIU/mL had detectable hTPO-Ab and five (50%) had hTg-Ab. Of the 65 participants with normal TSH values, 24 (37%) had hTPO-Ab present and 19 (29%) had hTg-Ab. An elevated TSH was, therefore, significantly associated with the presence of hTPO-Ab (Fisher exact test $p < 0.005$). The mean TSH in those patients with hTPO-Ab present was 7.2 μIU/mL compared to 4.7 in those without hTPO-Ab. This difference was statistically significant by two-tailed Student's *t*-test ($P < 0.02$) (**Table 3**). However, the titer of hTPO-Ab did not correlate with the TSH level (Fig.). No independent association was found between TSH and hTg-Ab.

There was no significant association between the presence or absence of either thyroid autoantibody and patient demographics, signs and symptoms, or other thyroid function tests, T4, T3, or T3 resin uptake values, based on chi-square analyses.

Goiter Patients. Thirteen patients had a clinically detectable goiter including two with palpable nodules. Three patients had increased serum TSH and two additional patients were receiving thyroxine replacement therapy, indicating that 5 of the 13 had significant thyroid failure (38%). Six of the goiter patients had one or the other thyroid autoantibody detectable, and these included the 5 patients with thyroid deficiency.

Discussion

As could be expected in an elderly population, symptoms of thyroid hypofunction such as memory loss, fatigue, depression, and constipation were prevalent but probably nonspecific. A goiter was present in 13 subjects, 8 of whom had never taken thyroid medication and who were clinically and biochemically euthyroid. Only one participant in the study group of 75 (1.3%) had symptoms and signs of over hypothyroidism.

Our results show a 13.3% prevalence of elevated TSH levels in ambulatory women over the age of 60 years. This finding substantiates those of Sawin et al. (4) and of Tunbridge et al. (3) and a large recent cross-sectional study of 1200 elderly patients (10). Both found a high prevalence of elevated TSH values in elderly women, 24% and 17.5%, respectively. These studies also noted a significantly lower prevalence rate in elderly men. Sawin et al. used the TSH upper limit of 5 μIU/mL to define an elevated TSH, which may explain the higher prevalence rates in his study. A New Zealand study which screened elderly persons over the age of 80 years using total T4 levels found 0.94% below normal (11). More cases of subclinical hypothyroidism might have been detected if TSH values had been examined. Since only one of ten women in our study with an elevated TSH level had a low T4 (10%), TSH is a far more sensitive screening test for hypothyroidism than T4. However, a prevalence of increased TSH values of only 2.6% was found in a previous United States study that did screen adults over 60 years of age with TSH (5). These authors did not indicate the ratio of men to women. As the prevalence of elevated TSH in men is lower than in women because of the lower prevalence of autoimmune thyroid disease in men, a male predominance in the sample may have contributed to this lower rate.

A more recent study in the United States (12) and several from other countries (3, 6, 7, 8, 10) document that 7%–45% of elderly subjects had hTPO-Ab or hTg-Ab or both. However, a variety of antibody techniques were used in these studies. Among surveys utilizing the same assays, the chosen upper limit of normal has varied, thus further limiting comparisons. In our study, the presence of thyroid autoantibody constituted a positive test. We found a 44% prevalence of hTPO-Ab in ambulatory women over the age of 60 years. In

TABLE 1
TSH versus Age and Thyroid Function Studies

	TSH < 7 (n = 65)		TSH > 7 (n = 10)		Total	
	Mean ± SD*	Range	Mean ± SD*	Range	Mean ± SD	Range
Age (years)	74.9 ± 7.7	61–87	71.8 ± 5.5	65–83	74.5 ± 6.6	61–87
T4 (μg/dL)	9.1 ± 1.6	4.9–13.5	7 ± 2.0	2.2–9.7	8.8 ± 1.8	2.2–13.5
T3 (mg/dL)	118.5 ± 28.2	75.8–255.1	112.7 ± 23.4	74.1–145.9	117.7 ± 27.5	74.1–255.1
T3RU (%)	37.5 ± 2.8	32.8–45.2	36.8 ± 2.9	33.0–41.8	37.5 ± 2.8	32.8–45.2
TSH (μIU/mL)					5.8 ± 4.6	1.0–28.6

* No significant difference between these two groups by Student's *t*-test.

the only other prevalence study in the elderly utilizing ELISAs (6), a rate of 18.5% was found, much lower than our 44% in a similar elderly female population. This study limited the positive hTPO-Abs to those participants with antibody titers greater than expected in an elderly control population. Since there is a higher prevalence of hTPO-Ab in the elderly, this population may not have been a suitable control group (6).

Our data support (8, 12) a significant association between an elevated TSH value and the presence of hTPO-Ab. However, our study and others (8, 10, 11) reveal that one-quarter to one-half of patients with hTPO-Ab present have normal TSH levels. Figure 1 illustrates the high antibody titers present in many subjects with normal TSH levels. Data are available suggesting that individuals with raised TSH and thyroid autoantibodies are at higher risk of developing thyroid failure (13), but the prognosis for those with high antibody titers and normal TSH levels has been less well documented. However, 90% of our subjects with subclinical thyroid failure (as evidenced by increased TSH levels) had detectable hTPO-Ab. Using a less sensitive antibody assay, another study (12) found a 67% prevalence of hTPO-Ab among persons with increased TSH values.

Hence, the clinical importance of hTPO-Ab in the presence of a normal TSH level and normal thyroid function still remains to be established but may be related to the subclass of the antibodies present (14). At present the only known correlation is with subclinical autoimmune thyroid disease, with evidence of mononuclear thyroid infiltration, the degree of infiltration correlating with antibody titer. Of interest, however, are observations that age itself is not directly related to the onset of thyroidal lymphocytic infiltration and that racial background may be of great import (15). Recent research suggests a link between characteristic thyroid autoantibody immunoglobulin G subclass distributions and titers and an inherited predisposition to thyroid disease (14). In the future, these may serve as markers for people at risk for developing clinical thyroid failure. However, women with an elevated TSH and the presence of thyroid hTPO-Ab have been found to have a 5% per year development rate of overt hypothyroidism (13). This development was cumulative, so that over a four-year period 20% were affected, and it was projected that over 10 years, 50% might develop clinical hypothyroidism. Further prospective studies are necessary to confirm such predictions in the elderly population, but one recent study followed such patients up for 12 months and found 18% of patients required thyroxine therapy during this time period (10).

TABLE 2
TSH versus Thyroid Antibodies

	TSH < 7 μIU/mL		TSH > 7 μIU/mL		Total	
	n	%	n	%	n	%
hTPO-Ab						
present	24	(37)	9	(90)	33	(44)
absent	41	(63)	1	(10)	42	(56)
hTg-Ab						
present	19	(29)	5	(50)	24	(32)
absent	46	(71)	5	(50)	51	(68)

While low TSH values in the elderly are often misleading and cannot be considered diagnostic of thyroid overactivity (10), the question of whether or not to treat an elevated TSH level in clinically euthyroid individuals has attracted much attention and is of major import in the elderly population, where coincident disease is more likely to be present. One retrospective study (16) found that normalization of an elevated TSH correlated with resolution of mild nonspecific symptoms of hypothyroidism, such as dry skin and easy fatigability. However, patients with a history of ablative thyroid therapy were studied, so that the results cannot be generalized to include other forms of

TABLE 3

Thyroid Antibodies versus Thyroid Function Studies

	hTPO-Ab		hTg-Ab	
	Present (x ± SD)	Absent (x ± SD)	Present (x ± SD)	Absent (x ± SD)
mean T4 (μg/dL)	8.8 ± 2.2	8.8 ± 1.4	8.7 ± 2.4	8.8 ± 1.4
mean T3 (mg/dL)	118.3 ± 33.4	117.2 ± 22.3	121.6 ± 35.5	115.9 ± 23.1
mean TSH (μIU/mL)	7.2 ± 6.4*	4.7 ± 1.7*	6.8 ± 6.8	5.3 ± 2.9

hTPO-Ab, thyroid peroxidase antibody; hTg-Ab, thyroglobulin antibody; TSH, thyrotropin.
* $P < 0.02$ by two-tailed Student's *t*-test.

hypothyroidism. More recent studies of cardiac function in similar patients showed marked improvement after thyroid hormone replacement (17). Since mild congestive heart failure is common in the elderly population, the treatment of subclinical thyroid failure may be of considerable importance.

In conclusion, our study of 75 women between the ages of 61 and 87 years revealed a prevalence of 13.3% of subclinical hypothyroidism, as evidenced by an elevated TSH level. Forty-four percent of the participants had hTPO-Ab and 32% had hTg-Ab. An elevated TSH was significantly associated with the presence of hTPO-Ab. No other significant relationships between the symptoms and signs of thyroid disease, thyroid function studies, or the presence of autoantibodies were found. We recommend screening of women over the age of 60 years for thyroid dysfunction, since the high prevalence of disease is not clinically apparent and may contribute to other major pathology such as cardiac dysfunction. A serum TSH level is the most sensitive and specific screening test available at this time and may be effectively linked with hTPO-Ab assessment to determine etiology of the thyroid failure.

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MRI Documentation of Hemorrhage into Post-traumatic Subdural Hygroma

John O. Lusins, M.D. and Ernest R. Levy, M.D.

Abstract

Rapid enlargement of a post-traumatic hygroma was demonstrated by MRI in a patient who had sequential studies performed after head injury. The enlargement was shown to be due to hemorrhage into the hygroma.

Accumulation of cerebral spinal fluid between the dura and arachnoid is a complication which may arise after head injury. Terms such as meningitis serosa traumatica, traumatic subdural effusion, and subdural hydroma also have been used to describe this condition. The most commonly accepted one is subdural hygroma.

The first clinical case to be described was that by Mayo in 1893 (1). Naffziger in 1924 (2) was the first to postulate that the cause of the excessive accumulation of the subdural CSF was due to a tear in the arachnoid at the time of the trauma. He proposed that the arachnoid tear acted as one way flap valve permitting CSF to enter but not leave the space. Therefore, the fluid would collect and the space enlarge. Gradual enlargement of a hygroma has been documented by both CT and angiography (3–6).

Recently, we had the opportunity to evaluate a patient with a post traumatic hygroma in whom the enlargement was not solely due to this flap valve postulate but rather due to bleeding into the hygroma collection.

Case Report. A 74-year-old man lost control of his vehicle and struck his head against the windshield, losing consciousness. He regained consciousness in the Emergency Room and returned to full mental function within two hours after the accident. A large laceration was noted on the back of the head.

The patient was admitted to the hospital for observation. On admission, the neurological examination failed to show any lateralizing findings. The patient had a CT scan which demonstrated the contusion in the occipital area and demonstrated a small but distinct frontal hyperlucency overlying the hemispheres and diagnosed as a left frontal hygroma (**Fig. 1**). The patient was followed up as an outpatient. The patient was seen a week later. At that time, the neurologic examination was negative and his mental status was normal. No headache was reported. A repeat MRI showed the hygroma collection to be present and only minimally changed from the previous study (Fig. 2).

It was elected to continue to observe the patient. The patient was seen two weeks later, at which time he was complaining of developing left-sided headache and some difficulty in concentrating. No lateralizing findings were noted. MRI showed significant enlargement of the subdural fluid collection, the fluid now being hyperintense on T1 and with a meniscus effect. A significant midline shift was noted (Fig. 3). The patient underwent surgery, and hemorrhagic fluid collection was removed. No membranes were noted. His postoperative course was uneventful.

Discussion. Although the first demonstrations of enlargement of a hygroma were through angiography, not until CT was readily available

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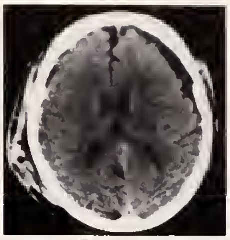

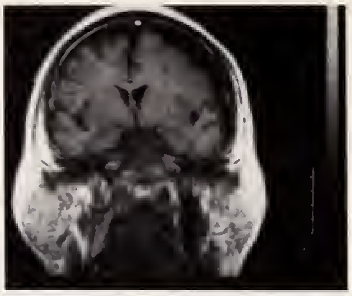

Fig. 1. **Left** CT obtained at time of injury shows left frontal hygroma in association with right occipital scalp contusion. Fig. 2. **Right** MRI sagittal T1 image performed a week after initial CT demonstrates previously diagnosed hygroma.

was a significant series collected. In the largest CT series by French et al. (5), the incidence of post-traumatic hygromas was 6.6% in a consecutive series of 1,601 patients with craniocerebral trauma. In that series, 54% of the cases (7 of 13) initially had a normal CT, only later developing the hygroma.

Since Naffziger's initial description of a tear in the arachnoid, numerous published reports have dealt with post-traumatic subdural hygroma. However, only in a relatively few instances have the authors been able to demonstrate at surgery an actual tear in the arachnoid (6, 7). Radionuclear studies, however, do lend credence to this postulate, since radioactively tagged albumen injected by lumbar puncture has been shown to gradually accumulate in the hygroma collection (6, 8).

In reviewing the literature, we are unable to demonstrate a case in which the hygroma is thought to enlarge by bleeding rather than by gradual spinal-fluid entrapment. However, a number of papers indicate that at surgery there is a spectrum of findings from purely clear cerebrospinal fluid in the hygroma to fluid that is xanthochromic or actually blood tinged (7, 9, 10). The phenomenon of enlargement by bleeding, however, has been demonstrated to occur in the case of sudden enlargement of chronic subdural hematoma (11). It is likely that both mechanisms may play a part in enlargement of a hygroma. As the entrapped CSF gradually enlarges the subdural space, the bridging veins are increasingly stretched and in certain cases may rupture, producing rapid enlargement of the hygroma.

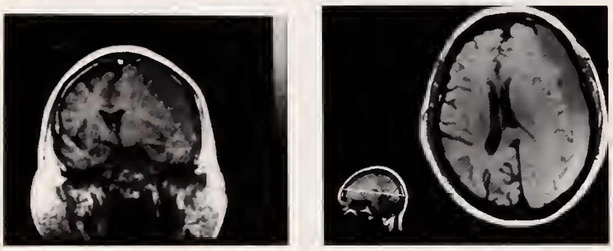

Fig. 3. MRI (**Left**) Sagittal and (**Right**) transaxial T1 images demonstrate enlargement due to hemorrhage into hygroma. Significant midline shift is present.

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A Case Report of Neurologic Improvement Following Treatment of Paraneoplastic Cerebellar Degeneration

Betty Jane Mintz, M.D., and David K. Sirota, M.D.

Paraneoplastic cerebellar degeneration (PCD) is a rare remote effect of cancer characterized by acute or subacute cerebellar dysfunction. Clinically, PCD is a syndrome of truncal and limb ataxia, sometimes associated with dysarthria and nystagmus. It occurs in less than 1% of patients with cancer (1). The onset of PCD may occur before or after the detection of a systemic malignancy. Pathologically, a profound loss of Purkinje cells is seen. In some patients with this disorder, an anti-Purkinje cell autoantibody has been found, termed anti-Yo (2, 3).

Seropositive and seronegative patients differ in regard to sex and type of malignancy (4, 5). Most seropositive patients are postmenopausal women with breast or gynecologic tumors. Seronegative patients can be male or female and have a wider range of tumors, including breast and gynecologic tumors, as well as Hodgkin's disease and lung carcinoma.

We report on a patient with this uncommon disorder who was somewhat atypical in several respects, including her response to treatment.

Case Report. A 70-year-old white woman had an enlarged, nontender right inguinal lymph node. Biopsy revealed metastatic adenocarcinoma. Further study showed enlargement of the left ovary.

The day after learning her diagnosis, she complained of sudden inability to control her legs. On neurologic examination, she was unable to stand, with or without assistance. There was no nystagmus. Rapid alternating movements, finger-to-nose, and heel-to-shin testing were normal. Vibratory sensation was diminished in the toes. The remainder of the examination results were normal, and the possibility of a conversion reaction was considered in the differential diagnosis. However, the next day she developed evidence of cerebellar dysfunction with marked impairment in finger-to-nose and heel-to-shin testing. She remained unable to walk even with assistance. Magnetic resonance imaging with contrast showed only minimal cerebral atrophy. On the basis of these findings, the diagnosis of paraneoplastic cerebellar degeneration was made.

The patient underwent pelvic exploration and was found to have a right tubal carcinoma with metastasis to the left ovary. A total abdominal hysterectomy and bilateral salpingo-oophorectomy was performed. Surgery was followed by a course of chemotherapy consisting of adriamycin, cisplatin, and VP16 given monthly for six months, followed by a single treatment with carboplatin.

Her serum anti-Yo antibody was negative on two occasions before treatment was begun. Carcinoembryonic antigen was elevated to the 20–30 ng/mL range and remained elevated after therapy was completed.

The patient was considered to be in complete remission after completion of chemotherapy. A CT scan of the abdomen and pelvis was negative. At this time, a marked improvement in her neurologic status was noted. She was able to stand unassisted and walk with a walker. Finger-to-nose and heel-to-shin testing returned to normal. Rapid alternating movements were within normal limits. As of the time of publication, she re-

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mains clinically free of carcinoma and continues to improve neurologically.

Discussion. Patients with PCD may have a range of initial cerebellar signs and symptoms, but some differences between seropositive and seronegative patients seem evident. In a recent review of 32 patients with PCD, the cerebellar disorder preceded the diagnosis of cancer in 75% of seropositive patients and 69% of seronegative patients. In 69% of seropositive and 38% of seronegative patients, the onset of the cerebellar syndrome was abrupt. In the rest, it was subacute. Vertigo and nausea followed by gait ataxia were the most common initial symptoms in the seropositive patients (5).

In another recent series of 47 patients with PCD, all seropositive patients had gait ataxia, limb ataxia, dysarthria, and nystagmus. All seronegative patients had gait ataxia and the majority had limb ataxia. In most seropositive patients, the diagnosis of PCD preceded the tumor diagnosis and in most seronegative patients, the diagnosis of PCD followed the tumor diagnosis. The antibody-positive patients were more likely to have an abrupt onset (4).

PCD typically follows an unrelenting course resulting in profound neurologic impairment. In one recent series, 75% of patients were confined to bed or wheelchair despite therapeutic attempts (5). In another series, improvement was noted in only 5 of 47 patients. Treatment of the underlying malignancy in the 18 patients with anti-Yo antibody did not result in improvement in their neurologic deficits. Two of these patients showed minor improvement with plasmaphoresis. Treatment of the underlying malignancy resulted in neurologic improvement in two seronegative patients, one with non-small cell carcinoma of the lung and one with Hodgkin's disease. A spontaneous remission of neurologic symptoms was noted in another seronegative patient with Hodgkin's disease. Plasmaphoresis did not appear to benefit any seronegative patient (4).

In a recent study, Furneaus et al. studied tumor cells from ten seropositive patients and ten patients with breast cancer who were normal neurologically. They found Purkinje cell antigens were expressed in the tumors from ten patients with PCD but not in the tumors of the neurologically intact patients. They concluded that the anti-Yo antibody results from an immune response to neural antigens expressed in tumors of patients with PCD. They further explain that since the brain has been felt to be an immunologically privileged site, antigens expressed in neuronal tissue may not have been presented to the immune system during the establishment of immune tolerance and may therefore be regarded as "foreign" by the immune system. When these antigens are expressed in tumor cells, a profound immunologic reaction may occur (6).

This pathophysiologic mechanism strongly suggests that early detection and treatment of the systemic malignancy offers the greatest hope for reversing the devastating effects of this disorder by eliminating the inciting antigen and blunting the ensuing immune response.

The patient presented here is unusual because her cerebellar syndrome responded so well to treatment of the malignancy. She is an example of early intervention leading to recovery of neurologic function.

Acknowledgments

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Introduction

David B. Sachar, M.D.
The Dr. Burrill B. Crohn
Professor of Medicine
Director
Division of Gastroenterology
Mount Sinai Medical Center

Frontiers in Gastro-Enterology

THIS ISSUE of *The Mount Sinai Journal of Medicine* commemorates a historic moment in the life of the Medical Center. For the first time in its 140-year existence, a division of Mount Sinai's Department of Medicine has been endowed and named for an individual. Even more meaningfully to us, this honor has been bestowed not on a faceless donor or a shadowy figure from the distant past, but on a colleague and contemporary, still professionally active, physically vigorous, and academically productive among us within shouting distance of octogenarian status.

Since retiring in 1983 from his quarter-century stewardship of Mount Sinai's Division of Gastroenterology, Henry Janowitz, clinical professor emeritus and consultant physician, has continued to play an integral role in the daily education of our gastrointestinal fellows and to stimulate a ceaseless flow of innovative clinical research. He is a superb clinician who has helped countless people, a researcher who has made fundamental contributions to our understanding and treatment of gastrointestinal disease, a teacher of some of the world's top gastroenterologists, and a friend to all of us.

In formal ceremonies on December 8, 1992, the President and Board of Trustees of the Mount Sinai Medical Center officially named the Dr. Henry D. Janowitz Division of Gastroenterology at Mount Sinai. To mark the occasion, hundreds of colleagues, present and former students, patients, and friends gathered in the Stern Auditorium to attend an international symposium on "Frontiers in Gastroenterology." Virtually the entire scientific program of that symposium is represented in this *Journal,* with major support from Kabi Pharmacia, a long-standing corporate friend of academic gastroenterology at Mount Sinai and throughout the world.

The unofficial dean of American gastroenterology, Joseph Kirsner, leads off with a historical perspective on Henry Janowitz's many contributions to the academic life-blood of our specialty. Specific examples follow of the seminal advances in basic and clinical gastrointestinal pathophysiology, spearheaded by three of Dr. Janowitz's former fellows: Peter Banks on pancreatitis, Eugene Straus on gastrointestinal hormones, and Lloyd Mayer on gastrointestinal immunology. Next, in a dazzlingly comprehensive yet crystal-clear overview, the world's leading figure in gastrointestinal clinical research, Professor John E. Lennard-Jones of London, discusses the evolution of the controlled clinical trial, an enterprise that has been much enriched by the activities of Henry Janowitz and his associates at Mount Sinai. Then, to exemplify the important applications of clinical trials and clinical experience to daily practice, Daniel Present concludes the formal program of the symposium with a spirited review of Mount Sinai's leading role in promoting advances in the treatment of inflammatory bowel disease.

Finally, fond reminiscences of Henry Janowitz's personal and intellectual impact are provided by half a dozen former students and other colleagues, from within our own walls to the farthest reaches of North and South America, the United Kingdom, and Australia. Indeed, five other articles in this issue—independent of this Festschrift—deal with gastrointestinal or hepatologic topics. This special issue of the *Journal,* therefore, bears witness to the fact that Henry Janowitz's imprint on gastroenterology at Mount Sinai—and, by extension, Mount Sinai's imprint on gastroenterology worldwide—are indelible.

Henry D. Janowitz and American Gastroenterology

Joseph B. Kirsner M.D., Ph.D., M.A.C.P.

I am deeply honored to represent the gastroenterology community in recognizing Dr. Henry Janowitz as physician, researcher, teacher, and humanist, as we dedicate the Dr. Henry D. Janowitz Division of Gastroenterology at the Mount Sinai School of Medicine and The Mount Sinai Hospital. Henry's outstanding career, now 54 years and counting, defies synopsis, and I am privileged to review his superlative record of achievement.

Henry David Janowitz was born in March 1915 in Paterson, NJ. His parents, with no formal educational background, encouraged Henry and his younger brother Morris to excel in school. The boys grew up in a loving home, deeply imbued with a reverence for learning and scholarship.

Henry's extraordinary intelligence and perseverance rapidly surfaced. In high school he wrote poetry, worked on the school paper, and in 1931, at age 16, crossed the Hudson River to take on Columbia College. Henry studied Shakespeare with Mark Van Doren, the poet; philosophy with Irwin Edman (a disciple of George Santayana) whom Henry revered; and Renaissance literature with Raymond Weaver. He attained Phi Beta Kappa and struggled with the opportunity to enter medical school or to accept a fellowship in philosophy.

Professor Edman earned himself a place, if only a footnote, in the annals of gastroenterology when he turned Henry away from philosophy. As Henry remembers, "Edman said to me one day: 'In philosophy one has to be a great philosopher, but there is always room for a good doctor.' " The wonderful irony is that Henry became a great physician-philosopher; a scholar who has provided inspiration and wisdom to countless colleagues and students. Henry's four years at the Columbia College of Physicians and Surgeons were a continuation of his undergraduate success. He made Alpha Omega Alpha and in 1939 graduated near the top of his class.

Henry's two years of house staff training at Mount Sinai in New York brought him into contact with many outstanding physicians. He spent a year in pathology with Paul Klemperer; and his imagination was fired by men like George Baehr, Isadore Snapper, Emanuel Libman, and Bela Schick, among others. World War II arrived and Henry joined the Army, serving for four and one half years. Assigned to Fort Smith, Arkansas, the young lieutenant reported for duty on the day that Thomas Urmy, the hospital's gastroenterologist, had been elevated to chief of medicine. Urmy, a disciple of the late Chester Jones of Boston, immediately designated Henry as the gastroenterologist and himself as Henry's preceptor.

After the war, Henry knew that he needed more training, more science, if he was to be a "real" gastroenterologist. He correctly assessed the trend in gastroenterology toward physiologic research and became associated with the late Morton Grossman in the Department of Clinical Science at the University of Illinois in Chicago. Henry's research produced a Master of Science thesis on the physiology of hunger and appetite, a field that he continues to follow. From Grossman

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Adapted with permission from J. B. Kirsner, Friedenwald Presentation to Henry David Janowitz, M.D. Gastroenterology 1984; 87:749–753. Adapted from the author's presentation at the Dedication of the Dr. Henry D. Janowitz Division of Gastroenterology on December 8, 1992 at the Mount Sinai Medical Center. From the Department of Medicine, University of Chicago. Address reprint requests to the author, The Louis Block Distinguished Service Professor of Medicine, University of Chicago Medical Center, MC 2100, 5841 South Maryland Avenue, Chicago, IL 60637-1470.

he also acquired some of the art of research and the excitement and satisfaction of successful investigation.

Returning to Mount Sinai, his inquisitive mind took him into several fruitful areas. With the noted physiologist Franklin Hollander, he investigated electrolyte secretions of the upper gastrointestinal tract. With the talented surgeon David Dreiling, he participated in highly productive research on the pancreas. Others at Mount Sinai who influenced Henry included A. A. Berg, the premier gastrointestinal surgeon, Richard Marshak, the skillful gastrointestinal radiologist, and for a short time, the brilliant Sol Berson. Confirming the sage observation of Sir Isaac Newton, "Discovery is never an isolated event; each discoverer stands on the shoulders of giants," Henry throughout had the foresight and the wisdom to associate himself with clinical and research giants.

In 1952, while continuing his research, Henry began his private practice in the office of Burrill Crohn, initiating a close association that lasted nearly 40 years. Henry opened his own office in 1958. At that time also, the late Alexander Gutman, chief of Medicine, asked him to establish the first division of gastroenterology at Mount Sinai Hospital. The challenge was formidable; but Henry's objective was clear from the start: a program that would encourage physicians to blend clinical investigation with excellent patient care, on a foundation of superb teaching. Thirty-five years later there are approximately 125 first-class gastroenterologists throughout the country and abroad who have been trained by Henry, many of whom have made important contributions to clinical and academic gastroenterology. To mention only a few: Jerome Waye (endoscopy), Irwin Sternlieb (Wilson's disease), Jack Hansky at Monash University in Sydney, Australia, Walter Dyck at The Scott and White Clinic in Texas, Peter Banks of Beth Israel Hospital, Boston, Burton Korelitz of New York, Arthur Lindner of New York University, and David Sachar, the B. B. Crohn Professor of Medicine at Mount Sinai and the man who succeeded Henry in July 1983 as head of the Division of Gastroenterology at Mount Sinai.

Research, training, care of patients, participation in local and national societies—Henry approached every task with the zeal of Tennyson's Ulysses, determined "to strive, to seek, to find, and not to yield." His major research interests and accomplishments have been in hunger and appetite, electrolyte secretion by the upper gastrointestinal tract, pancreatic physiology, and inflammatory bowel disease. He pioneered in examining the role of the upper gastrointestinal tract in the regulation of food intake. He was the first to document the stimulating effect of secretin on the electrolytes of bile. He persevered in establishing the role of carbonic anhydrase in the secretion of hydrogen ions by the gastric parietal cells after this relationship had been abandoned by prominent physiologists. His studies of gastric function in a patient with a gastric fistula paralleled the classic observations of Beaumont and others.

Dr. Janowitz was the first investigator also to authenticate the safe inhibition of pancreatic secretion by the carbonic anhydrase inhibitor Diamox; the first to demonstrate the direct damaging effect of alcohol on the pancreas, and the first to establish inhibition of lipoprotein lipase as one of the mechanisms of the hyperlipidemia complicating acute pancreatitis. These and other original observations culminated in an important book, *Pancreatic Inflammatory Disease.*

Henry's association with Dr. Crohn kindled a highly productive interest in inflammatory bowel disease, including important studies on toxic dilatation of the colon in ulcerative colitis, statistical precision in defining recurrence rates in Crohn's disease, the intestinal and extra-intestinal manifestations of inflammatory bowel disease, the usefulness of therapeutic measures including ACTH and hydrocortisone, and quality of life after surgery for Crohn's disease. His approximately 300 publications are models of perception and scientific rigor.

Editing various journals constitutes yet another major career of Dr. Janowitz. He has served as editor or as a member of the editorial board of the *Handbook of the American Physiological Society,* the *American Journal of Chronic Diseases,* and the *American Journal of Physiology,* and as chief editor of the revived *American Journal of Digestive Diseases* (now known as *Digestive Diseases and Sciences*), and the *Proceedings of the Society for Experimental Biology and Medicine.*

Henry has been an active member of many prestigious societies: the American Physiological Society, the American Society for Clinical Investigation, the Association of American Physicians, the Society for Experimental Biology and Medicine, the American Society for Clinical Nutrition. He has been president of the New York Gastroenterological Association and a member of the American Board of Gastroenterology. He is a founder and for seven years was the first chairman of the Scientific Advisory Board of the National Foundation for Ileitis and Colitis.

He joined the American Gastroenterologic Association (AGA) in 1952 and has been secretary, vice president, and president. His tenure in office was characterized by innovation and activity. The Second Conference on Digestive Diseases as a National Problem (April 23–25 and May 18, 1973) was initiated by Dr. Janowitz, "who believed that the field of digestive disease should be re-examined and perhaps stimulated as it was by the earlier conference of 1967."

In 1973 also, Dr. Janowitz created the AGA Presidential Commission on the Status and Future of the AGA, with the charge "to undertake a critical review of the Association's organization, functions, and policies, financial resources, the relationship of the AGA with the National Institute of Arthritis, Metabolism, and Digestive Diseases, the government, and with international gastroenterology, the possibility of a National Voluntary Organization for Digestive Diseases, and future goals. The Janowitz Presidential Commission is credited with stimulating the recent spectacular growth of the AGA, and its recommendations continue to influence gastroenterology today.

Involvement with the AGA has been one of the great pleasures of Henry's scientific and personal life: "It was not merely the exchange of information or even doing good for gastroenterology, but the personal contacts with my many friends over the years that provided such a rich source of satisfaction." In 1984 I had the distinct pleasure, on behalf of the American Gastroenterological Association, to present to Henry its most treasured honor, the Julius Friedenwald Medal, in recognition of his many contributions to the science and practice of gastroenterology.

Henry is in demand as a speaker in this country and abroad. He has been the McArthur Lecturer at the University of Edinburgh, the Comfort Lecturer at the Mayo Foundation, and visiting professor at many medical centers and universities.

A major strength of Henry's career has been the great supportive and complementary role played by his accomplished family, his wife Adeline (Addie), and their two daughters, Mary and Annie. His late brother, Morris, one of the nation's leading sociologists, was the Lawrence A. Kimpton Distinguished Service Professor at The University of Chicago.

Addie Janowitz is a student of trends in modern art and is a widely recognized Henry James scholar. She is the editor of the *Henry James Journal* and the *Journal of Pre-Raphaelite Studies*. Throughout, Addie has been a colleague and champion of Henry's work and her literary activities have maintained Henry's scholarly interest in literature.

Their daughter Mary, a graduate of Barnard College, lives in San Francisco with her husband and their two children. Annie studied at Oxford and has a Ph.D. in English literature from Stanford University. She has taught at Smith College and is a newly appointed assistant professor at Brandeis University. These family activities provide Henry access to the latest in literary thought. His intellectual curiosity is enormous; and a satisfying vacation consists of settling down with Fitzgerald, Hemingway, or Faulkner.

Henry's impressive bibliophilic talents would easily qualify him as the literary critic of *The Times* of London, the *Manchester Guardian,* or the *New York Times.* Indeed, such contributions as "Marius the Epicurean in T. S. Eliot's Poetry," "An Anglo-American Consultation: Sir William Osler Refers Henry James to Sir James MacKenzie," (with Adeline R. Tintner), and "Falstaff's Nose *Was* 'A Table of Green Fields': A Footnote to Ephim Fogel's Defense of the Folio Reading in Cahiers Elisabethains" place Janowitz in the company of such distinguished physician-litterateurs as Oliver Goldsmith, A. Conan Doyle, and W. Somerset Maugham. And they lacked his medical and scientific achievements.

This brief account only hints at Henry's achievements. Like Henry James, his artistry has been subtle and deep. In moments of self-evaluation, he claims to be able to "only think about one thing at one time," which for most of us would be a considerable feat. He obviously has thought about many things, each in their own time; in each instance the outcome has been new knowledge, and a brightening of the path of scientific endeavor.

Having turned over the leadership of his division at Mount Sinai School of Medicine to David Sachar, he remains as clinical professor of medicine, co-director of the Gastroenterology Disease Unit, and director of the Burrill Crohn Foundation. He continues his "normal" 12-hour daily schedule as a clinician, consultant, teacher, clinical investigator, and author.

His sought-after clinical preceptorship, accommodating four fellows annually, each for three months, is a model of personalized training. The fellow begins the day at 7:30 AM in Dr. J's office, then accompanies Henry on hospital visits, rounds, and conferences. Henry's 1992 paper, "The Art of the Gastrointestinal Consultation," reflects this extensive clinical experience, and his conclusion that "gastroenterology is still an active transaction between doctor and patient" epitomizes the ethos of gastroenterology. Henry's clinical research program currently emphasizes the metanalysis of clinical data on the natural history and the treatment of IBD. His 1985 publication, *Inflammatory Bowel Disease: A Personal View,* reflects this long experience. His clinical achievements have been recognized in the 1986 Stuart Distinguished Lecture and in the 1992 Clinical Achievement Award from the American College of Gastroenterology. His contributions to the medical literature continue: *Your Gut Feelings: A Complete Guide to Living Better with Intestinal Problems* (1987), *Indigestion* (1992), and another on IBD scheduled for 1993 publication.

How does he do it? Where does he get the motivation and the energy to accomplish so much? A partial answer probably is to be found in what William Osler considered a master-word in medicine: Work, "the open sesame to every portal; the true philosopher's stone which transmutes the base metal of humanity into gold . . . and the touchstone of progress." Another part of the answer is in Henry Janowitz's unwavering commitment to excellence, searching imagination, disciplined inquiry, reasoned judgment, and appreciation of originality.

My own admiration for Henry is unbounded. He has demonstrated over the years the qualities of intellect, commitment, and integrity that bespeak the philosopher-physician, a valued tradition. He has shown that important research could be carried out successfully by physicians proficient in both the art and the science of patient care, and that this combination enhances the clinical relevance of the research.

Henry, the dedication of the Division of Gastroenterology in your name is a well-deserved and uniquely appropriate recognition of your outstanding accomplishments, and also honors the Mount Sinai School of Medicine. The entire gastroenterologic community joins me in extending to you our warmest congratulations and best wishes for the future.

Modern Concepts in Pancreatitis

Peter A. Banks, M.D.

Although I completed my fellowship in gastroenterology at The Mount Sinai Hospital 25 years ago, I never really left Mount Sinai. On a personal level, friendships I developed while in training have been an important part of my life for the past 25 years, and I trust will continue for at least another 25 years. On a professional level, the lessons I learned at Mount Sinai will endure for a lifetime. The educational environment was stimulating and exciting, and it included input not only by gastroenterologists, but also by surgeons, radiologists, pathologists, nutritionists, and many other specialists.

I would call attention to two lessons in particular that are the special legacy of Dr. Janowitz. The first lesson was to think critically. Whether presenting at our weekly physiology seminar on Saturday morning or at the bedside, you had to know your stuff, and you had to think critically. The second lesson was to develop intellectual curiosity. Largely due to the impact that Dr. Janowitz had on all of his fellows, we learned to probe deeper, learn more, and do more. These lessons, and many more taught by Dr. Janowitz, inspired me to make the additional efforts to teach and to engage in clinical research. It was at The Mount Sinai Hospital that I was stimulated to explore the mysteries of the pancreas.

The field of pancreatitis has advanced rapidly. In acute pancreatitis, new information has been gathered on the cell biology of pancreatitis (1, 2) and mediators of inflammation (3–16). There have also been advances in the diagnosis of acute pancreatitis by CT scan (17–20), early recognition of infected necrosis by guided percutaneous aspiration (21–23), increased awareness of the threat of sterile necrosis (24–27), and improvements in treatment (21, 24, 28–32). In the field of chronic pancreatitis, there is increased understanding of the causes of pain (33–38) and potential improvements in the treatment of pain (39–43). These advances will be described briefly.

Acute Pancreatitis

Cell Biology. Digestive enzymes as well as other proteins, including lysosomal hydrolases, are synthesized on ribosomes attached to the rough endoplasmic reticulum and transported to the Golgi complex. As they traverse the Golgi complex, hydrolases that are transported to lysosomes are sorted from other proteins via chemical alterations and are then bound to mannose-6-phosphate receptors. Once they reach the lysosomal compartment, the lysosomal hydrolases dissociate from their receptors. In comparison, digestive enzymes pass through the Golgi complex, are packaged in condensing vacuoles, mature into zymogen granules, and migrate to the apical cell surface. Zymogens then fuse to the apical cell surface and discharge enzymes into the lumen.

A number of protective mechanisms prevent premature activation of pancreatic enzymes. First, maturation of digestive enzymes and lysosomal hydrolases occur via separate pathways. If they travelled along the same pathway, the lysosomal enzyme, cathepsin-β, could potentially activate trypsinogen to trypsin. Second, digestive enzymes and lysosomal hydrolases travel within membrane-enclosed compartments. Third, digestive enzymes that have the potential of injuring acinar cells are synthesized, transported, and secreted as proenzymes. Fourth, a trypsin inhibitor travels with digestive enzymes to prevent the premature activation of trypsinogen to trypsin. Fifth, pH within zymogen granules is acidic. An

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acid pH inactivates any trypsin that might be prematurely activated from trypsinogen. Sixth, within the lumen of the pancreatic ducts, any trypsin that might be activated is either inhibited by the trypsin inhibitor or degraded in the alkaline pH.

Several experimental models of acute pancreatitis produce similar injury within acinar cells (1, 2). In one model, that of diet-induced pancreatitis, mice fed a diet that is choline-deficient and ethionine-enriched develop fatal pancreatic necrosis. In another model, that of secretagogue-induced pancreatitis, rats administered a supramaximal dosage of the cholecystokinin analogue, cerulein, develop a reversible form of interstitial edematous pancreatitis.

In both of these models, the pathophysiology of acinar cell injury takes a similar form. The initial event leading to this injury is a blockage of secretion resulting in accumulation of zymogen granules within acinar cells. The next step is a fusion of lysosomes and zymogens within large vacuoles. Activation of pancreatic enzymes presumably then takes place because these vacuoles now contain both lysosomal hydrolases (including cathepsin-β) and digestive enzymes. Once cathepsin-β activates trypsinogen to trypsin, trypsin can then catalyze many proenzymes to their active form. Since these vacuoles that contain both lysosomal hydrolases and pancreatic enzymes are quite fragile, activated enzymes are then released into the cytoplasm and cause intracellular injury.

Colocalization of lysosomal and digestive enzymes can also be demonstrated in acinar cells of the rabbit or rat following pancreatic ductal ligation, but acute inflammation does not occur. Hence, there appears to be a spectrum of inflammatory responses when there is colocalization, ranging from absent (no inflammation) to mild interstitial edema to fatal necrotizing pancreatitis.

The relevance of these findings to human pancreatitis remains uncertain. Additional experimentation will be needed to determine whether these experimental models accurately reflect the earliest changes in human pancreatitis, and if they do, whether a strategy can be developed to prevent intracellular injury.

Mediators of Inflammation. It is known that pancreatic enzymes such as phospholipase-A_2 and elastase injure pancreatic parenchyma. A variety of synthetic inhibitors of trypsin, inhibitors of other proteases, and inhibitors of phospholipase-A_2 have been shown in experimental pancreatitis to reduce inflammation and at times improve survival, but studies in humans have not yet been conducted (3–6).

Also, a variety of mediators of inflammation may play a role in intensifying or perpetuating an inflammatory response:

- Oxygen-derived free radicals
- Platelet-activating factor
- Neutrophils
- Leukotrienes
- Complement
- Cytokines
- Prostaglandins
- Endotoxin

The role of these potential mediators in acute pancreatitis remains to be clarified. For example, in some reports on experimental pancreatitis but not others, oxygen-derived free radicals have been thought to be significant mediators of cell injury (7–9). In addition, inhibitors of neutrophil migration and antagonists of platelet-activating factor have been shown experimentally to reduce inflammatory response (10, 11). Activation of complement may play a role in the development of multiple system organ failure (12). In addition, there has been speculation that acute pancreatitis may induce a cytokine response that intensifies the inflammatory response and increases susceptibility to sepsis. In one report, patients with severe acute pancreatitis exhibited very high levels of interleukin-6 in serum (13). Studies with prostaglandins have yielded different results on the natural history of experimental pancreatitis. Some prostaglandins appear to be helpful, whereas others increase microvascular permeability and increase the severity of pancreatitis (14–16). Thromboxane-A_2, by its properties as a vasoconstrictor and stimulator of platelet aggregation, appears to worsen experimental pancreatitis, and its effects can be blocked by a potent inhibitor (14).

In summary, a considerable amount of work will be required to define the role of these potential mediators of inflammation in the natural history of acute pancreatitis and to develop ways to counteract their impact.

Role of CT Scan. The use of CT scan with intravenous contrast utilizing bolus technique has had an enormous impact on our ability to care for patients with acute pancreatitis (17–19). Following intravenous contrast with bolus technique, uniform perfusion of the pancreas indicates that the microcirculation of the pancreas is intact and that the process is interstitial pancreatitis. When portions of the pancreas enhance poorly following bolus injection, these poorly perfused or nonperfused areas are thought to represent areas of necrosis or fluid. The larger the areas of nonperfusion, the more confident is the clinician that the patient has necrotizing pancreatitis. It is much more difficult to ascertain on CT scan whether inflammatory changes in the peripancreatic tissue represent fluid or necrotic fat. If Hounsfield units are in the range of 0–15, the likelihood is that these areas represent fluid. When Hounsfield units exceed 15, peripancreatic necrosis is more likely.

The significance of pancreatic necrosis lies in the increased risk of mortality associated with it (20). In interstitial pancreatitis, even when associated with systemic complications, mortality should be less than 5%, assuming proper care of the patient. Mortality in necrotizing pancreatitis is much higher. The overall mortality in sterile necrosis is 10%, but in infected necrosis it is 30%. Mortality in necrotizing pancreatitis increases further in the presence of systemic complications. That is, in sterile necrosis with severe systemic complications such as shock, respiratory insufficiency, or renal insufficiency, the mortality may be 30%–40%. In infected necrosis, with similar systemic complications, the mortality may be greater than 50%. Hence, the interplay between CT appearance and the presence or absence of systemic complications helps the clinician assess the severity of acute pancreatitis.

Infected Necrosis. Many if not most deaths in patients who have acute pancreatitis are associated with infected necrosis of the pancreas (20). One important reason for the high mortality is delay in surgical debridement. During the past ten years, Stephen Gerzof and I have worked together establishing the role of guided percutaneous aspiration in the early diagnosis of infected necrosis. In our updated experience with 87 patients strongly suspected of harboring pancreatic infection on the basis of a CT scan showing severe pancreatitis (Balthazar-Ranson score of D or E), extreme systemic toxicity (usually a very high white count of 20,000–30,000 and temperature 102°F–104°F), 44/87 patients were indeed infected.

We have learned that guided percutaneous aspiration is a safe accurate method in the early diagnosis of pancreatic infection, that infection occurs early in acute pancreatitis, that both fluid and necrotic tissue are infected, and that early surgical debridement offers the best chance in reducing mortality (21–23).

Sterile Necrosis. As I have continued to evaluate the outcome of patients with necrotizing pancreatitis, I have been impressed that patients with severe sterile necrosis who appeared extremely toxic on the basis of systemic complications also have high mortality. I have sought to identify prognostic factors that might help explain this high mortality. As a result of observations on 26 patients with sterile necrosis, all of whom had at least one systemic complication, I have established several unfavorable prognostic factors that correlate with high mortality (24), including:

- Very high Ranson's score and APACHE-II scores within the first 48 hours
- Development of multiple systemic complications
- In particular, the development of shock, which was the best predictor of a fatal outcome; in our experience, almost all patients who eventually died experienced shock within the first 7–10 days of hospitalization.

On the basis of this information, we can now sort out patients who can be expected to survive with intensive care from those who have a high likelihood of a fatal outcome. Although the role of surgery in sterile necrosis of the pancreas remains controversial, in my view, patients with unfavorable prognostic factors should undergo surgical debridement until such time as more effective medical treatment is found that improves mortality.

In the context of sterile pancreatic necrosis, it has become increasingly clear that a fluid-density mass may replace pancreatic parenchyma and be erroneously interpreted as pancreatic pseudocyst (25, 26). In our experience with 17 patients, almost all intrapancreatic fluid-density masses contain a considerable amount of necrotic debris as well as fluid (27).

The therapeutic implication of this finding is important. Whereas pancreatic pseudocysts that extend out of the pancreas contain mostly fluid and only a scant amount of necrotic debris and can be treated by surgical decompression and at times by either pigtail catheter drainage or endoscopic cyst-gastrostomy, neither endoscopic nor radiologic techniques should be attempted for intrapancreatic fluid density masses. The reason is that these techniques are not able to remove necrotic debris. Failure to eliminate this debris leads to secondary intrapancreatic infection. In our experience, all patients with intrapancreatic fluid density masses treated by surgical debridement did well; those treated with endoscopic or radiologic techniques became secondarily infected and eventually required surgical debridement.

Treatment. Infected necrosis requires surgical debridement. In sterile necrosis, the role of surgical debridement remains controversial (24). Prophylactic antibiotics have recently been shown to reduce the incidence of pancreatic infection but not to improve mortality (28). Endoscopic sphincterotomy has been recommended in severe gallstone pancreatitis (29). Although morbidity was improved in elderly patients with severe gallstone pancreatitis, it is possible that this improvement related more to eradication of biliary sepsis than to improvement in the pancreatitis itself. Efforts should be made to protect the microcirculation of the pancreas (30, 31). In one study, low-dose dopamine was helpful in the experimental animal in reducing microvascular permeability (30). Methods to improve phagocytic function may prove to be helpful (32).

Chronic Pancreatitis

Causes of pain in chronic pancreatitis include superimposed acute parenchymal inflammation, neural inflammation, and increased intrapancreatic pressure (33–38). It appears that pancreatic nerves are not trapped or squeezed by fibrosis but are actually larger than normal (34). In addition, elegant ultrastructure studies have shown that there is a disruption of the perineurial sheath that shields the internal neural components from surrounding tissue (34). Once this sheath has been disrupted, inflammatory cells can then invade nerve tissue and may evoke an inflammatory response by discharging enzymes directly into nerve bundles.

In addition, there is increasing evidence that intrapancreatic pressure is increased in acute pancreatitis (36–38). This increase may be sufficient to reduce capillary filling and even induce tissue acidosis (38). It is conceivable that pain results from these phenomena and may possibly involve the formation of oxygen-derived free radicals (39).

Treatment of Pain. The treatment of pain in chronic pancreatitis includes discontinuation of alcohol and the administration of analgesics.

If the pain has as its basis an ischemic event, allopurinol may play a role in its treatment (39). We are now embarking on a randomized, prospective, double-blind trial of the use of allopurinol in treating the pain of chronic pancreatitis.

A third method is to suppress secretion with drugs (omeprazole or an H_2 blocking agent) or pancreatic enzymes. Although some reports have reported encouraging results with pancreatic enzymes, their effectiveness seems best among patients with idiopathic pancreatitis and much less among those with alcoholic pancreatitis (33).

Efforts to modify neural transmission by drugs or a nerve block have, in general, not been effective.

Methods to relieve obstruction now include the use of stents (40, 41), lithotripsy (42), and surgery. The use of stents to overcome a stricture has become widespread. There is increasing concern that stents may induce ductal changes that resemble those of chronic pancreatitis (43). Lithotripsy has also been reported to be beneficial in the treatment of pain of chronic pancreatitis (42). Although these studies are encouraging, they have not been performed in a randomized, prospective, double-blind fashion. Hence, among the various proposed therapies to overcome ductal obstruction, none has been convincingly shown to be effective.

Summary

A great deal remains to be learned about the pathophysiology, natural history, and treatment of acute and chronic pancreatitis. As we consider problems in treatment, we would be well advised to consider these words of Dr. Henry Janowitz: "Gastroenterologists are physicians who know how to think about and manage patients who have gastrointestinal problems." (44). To the extent that we heed these words and always give serious thought to what we are trying to achieve, we will provide greater help for our patients.

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New Frontiers in Gastrointestinal Hormones

Eugene Straus, M.D.

History is alive at Mount Sinai Medical Center, and even those of us who have played the smallest roles take interest and pride in that process. Gastroenterologists can take special pride, as this event and all that it signifies calls attention to rich traditions in the area of digestive diseases. As one who trained at Mount Sinai, and I am honored to be a representative of the many outstanding gastroenterologists who drank at this well of knowledge, curiosity, and fellowship, deep feelings are aroused when I look around this room and see my teachers, people who are still informing and inspiring us. Henry Janowitz is foremost in this tradition.

Dr. Kirsner speaks of Henry's contributions to gastroenterology. We each know many of these, and others, because he made so many important contributions, and I am thinking now of his early work in gastric secretion of mucus, which I recently came across in Horace Davenport's forthcoming *History of Gastric Secretion and Digestion.*

We also each cherish our personal experiences with this man of extraordinary experience and wisdom. I remember my first meeting with Dr. Janowitz. In my naiveté I was expecting to discuss inflammatory bowel disease in a setting of opulence and refined taste. I was pleasantly surprised to find him working on a manuscript in a most dingy little cubby on what I remember to be the third floor of Atran. We discussed "Washington Square" and *The Real Thing*. There was an abundance of refined taste, and it was all the professor's.

On such an occasion it is well to try to put things into perspective. Let me review briefly the march to New Frontiers in gastrointestinal hormones before trying, even more briefly and certainly with even less authority, to look down the road ahead.

The Old Frontier

It was the first piece of good Yankee science and its symbolic beginning came when the farmer's son from Lebanon, Connecticut declined an offer of land to farm for himself and rode out on the new mare, fondling the $100 in the leather pouch which was the second part of papa's parting gift. William Beaumont's formal training was a two-year apprenticeship with Dr. Benjamin Chandler of St. Albans, Vermont, beginning in 1810. His independent and adventurous nature, along with his dedication to his patient, the reluctant Alexis St. Martin, and to meticulous observation, begin and define the great tradition of physician investigators in this country. His *Experiments and Observations on the Gastric Juice and the Physiology of Digestion,* published by F. P. Allen of Plattsburg, NY, in 1833, was read throughout the world and opened the modern study of digestive processes. Beaumont stimulated countless physician investigators, including Osler and Henry's professor, Andrew Conway Ivy, both of whom wrote introductions to Myer's *Life and Letters of Dr. William Beaumont.* I read the *Experiments and Observations* as a first-year fellow and remember discussing it with Dr. Janowitz, whom I revered in the direct chain from Beaumont through my own professors: Janowitz, Schaffner, Sachar, Lieber, Levine, Berson, and Yalow, and I was inspired to follow. If our country

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cannot restore a greater sense of purpose and stability to life within this tradition, there will be fewer New Frontiers here.

Pavlov's extensive studies of digestion centered around the issue of regulation of functions, and by 1902 his doctrine of "nervism" was widely accepted. At University College in London William Bayliss and Ernest Starling decided to denervate the dog pancreas and, on the "great afternoon" of 16 January 1902, the brothers-in-law achieved regulation of water and bicarbonate secretion by injecting extracts of duodenal mucosa. Starling declared that they had discovered "a chemical reflex." They began describing their findings before the Royal Society within a week (1, 2). They called their chemical messenger secretin, and some three years later, at the suggestion of William Hardy, Starling coined the term "hormone."

Pavlov, always the scientist, had someone in his laboratory repeat the secretin experiment and quickly concluded that Bayliss and Starling were right. While most were convinced that the duodenum released a chemical messenger in response to acid, there were skeptics, and even Ivy considered that secretagogues might be contained within food until his transplantation experiments of 1927 (3).

Standing on the shoulders of giants, John Sydney Edkins of St. Bartholomew's Hospital Medical School set out to find a "gastric secretin," and by 1905 he reported the discovery of what he called "gastrin" to the Royal Society (4). We know too that by 1920 there was general agreement that gastrin did not exist, that Edkins' crude extracts contained histamine, and that it was histamine which had caused his cats to secrete acid. Poor Edkins, he had done good work, he had noted the vasodilator activity of both his oxyntic and antral mucosal extracts, and the fact that only the antral extracts stimulated secretion. Certainly both extracts had contained histamine, but intravenous injection of histamine in the concentrations likely to have been present in his extracts does not stimulate acid secretion. I believe that he died in a state of scientific rejection. Postmortem rehabilitates.

In 1928 the cross-circulation experiments of Ivy and Oldberg extended the earlier observation of Okada who, working in Starling's laboratory, had found that intestinal acidification resulted in contraction of the gallbladder (5, 6). Active material was extracted from duodenal mucosa and was named cholecystokinin (CCK). Fifteen years later Harper and Raper demonstrated that intravenous injection of intestinal extracts stimulated the secretion of pancreatic enzymes (7). They named the hormonal material responsible for this activity "pancreozymin" (PZ). In 1966 Jorpes and Mutt purified the crude material and demonstrated that CCK and PZ were the same peptide (8). It is now conventional to use the term CCK.

The Middle Frontier

One might consider that the Old Frontier in the field of gastrointestinal hormones began with the discovery of secretin and the conceptualization of the endocrine system by Bayliss and Starling and extended through the appreciation of the three well-accepted gastrointestinal hormones secretin, gastrin, and CCK. The closing of the Old Frontier was marked by the new developments which opened the Middle Frontier: advances in protein chemistry and radioimmunoassay (RIA), which allowed the ready purification, sequencing, and synthesis of peptides, and the evaluation of their status as hormones. This occurred in or about the late 1960s. Now the flow of scientific events reversed from the classic approach of Bayliss and Starling. No longer did we begin with the physiologic action, such as the secretion of water and bicarbonate, and proceed to the identification of the hormone, for example, secretin. In the new mode we purify, sequence, and synthesize peptides and then look for their physiologic roles.

The Middle Frontier was thus marked by the appearance of what Mort Grossman called the Candidate Hormones (9). The application of RIA methodology allowed the analysis of hormonal significance and the rapid characterization of heterogeneous molecular forms. But perhaps the most intriguing concept of the Middle Frontier was that the peptides could be more broadly distributed and function by nonhormonal modes.

It was found, for example, that gastric inhibitory polypeptide (GIP) is not an enterogastrone, but probably has a hormonal role as an incretin and might better be called glucose-dependent insulin-releasing peptide. Vasoactive intestinal peptide (VIP) was detected in many tissues and is not a hormone at all but a neuropeptide. But CCK proved to be most instructive for the emerging conceptualizations of the Middle Frontier.

At first there was little interest in CCK. Much more work was done with the closely related gastrin peptides. The source of gastrin's appeal was in its applicability to the study of acid-peptic disorders. No such obvious rewards were available to underwrite the more arduous technical work required for sensitive and specific measurement of CCK peptides, since no clinical states of excessive secretion of pancreatic enzymes, hepatic bile flow, or gallbladder contractility had been defined or postulated. But then, in the middle seventies, CCK was found in the central nervous system (10). As a venerable gastrointestinal hormone, CCK inspired respect but little enthusiasm. Found in a new and unexpected location it seemed more exciting. Adding to the excitement were the high concentrations throughout the cerebral cortex and subcortical areas, the abundance of the COOH-terminal octapeptide, the concentration of immunoreactivity in synaptosomes, and the release from synaptosomes according to paradigms usually employed to evaluate neuronal chemicals purported to have a role in synaptic physiology.

In a sense the end of the Middle Frontier brings together the concepts of the Old Frontier. Nervism was an incomplete understanding of the regulation of digestive organ function. With the discovery of hormones it appeared that two rather disparate systems regulated function: the nervous and endocrine systems. Here at the end of the Middle Frontier we can see how closely related these seemingly disparate systems are. The very same peptide, CCK, is synthesized in both endocrine cells and neurons and regulates function both as a hormone and as neurotransmitter. We understand how venerable the peptides are as an information transfer system, how many biologically active sequences have been conserved through evolution, even though these sequences may have been included in new cell types and taken on new modes of activity and biological roles. A messenger may have begun as an autocrine or paracrine agent in a simple organism and then developed hormonal and/or neuronal actions in more complex forms. This is why the term “gastrointestinal hormones” has given way to “regulatory peptides.” Finally, of course, the tremendous insights into the regulation of gene expression are a part of the Middle Frontier period as well, although the greatest contributions of molecular biology to this field lie ahead.

The New Frontiers

What of the New Frontiers in gastrointestinal hormones? This is an even more artificial and speculative construct than my already straining Old and Middle frontiers, but allow me to make a fool of myself in public. There will be no discovery of an essential hormone like insulin in the treasure trove of regulatory molecules found in the gastrointestinal tract. This would appear evident from the fact that the removal of virtually the entire alimentary canal does not require the replacement of an essential hormone. Nonetheless, important regulatory humors will continue to be discovered, and I expect that the liver will be the source of some of these. Perhaps a factor regulating renal cortical blood flow will be found.

The future will certainly include development of our knowledge of brain-gut relationships. This will grow from studies of the interactions of regulatory peptides acting as paracrine, hormonal, and neurotransmitter agents. The ability to make electrophysiologic recordings of single visceral afferent fibers, the use of the selective sensory neurotoxin, capsaicin, refined immunohistochemical techniques, and other methods will facilitate these studies. We will see the definition of the roles of substance P (SP) and calcitonin-gene-related-peptide (CGRP) in visceral afferent neurons. We will see thyrotropin-releasing factor (TRH) emerge as a player in the vagal regulation of gastrointestinal function. Corticotropin-releasing factor (CRF) will be extensively studied for its role in stress-related alterations of gastrointestinal functions. And the interrelationship between CCK released from the gut as a hormone, and brain CCK in satiety mechanisms will be worked out.

Of course, as always in science, the most important and exciting developments will come as a complete surprise. That’s the fun of it all.

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Current Advances in Gastrointestinal Immunology

Lloyd Mayer, M.D.

Although the initial descriptions of the inflammatory bowel diseases are, in the case of ulcerative colitis, more than 100 years old, and in the case of Crohn's disease more than 50 years old, surprisingly little progress has been made toward a firmer understanding of their pathogenetic mechanisms. The histopathologic features offer clear evidence of an active ongoing inflammatory and immune response. However, the question remains: What is driving these responses? Thus far, despite grand-scale efforts, no consistent pathogen has been isolated from the tissues of patients with inflammatory bowel diseases, nor have newer sophisticated technologies yielded evidence for unusual viral or bacterial forms. We are left, then, in the same predicament facing investigators studying chronic inflammatory disorders of other organ systems (rheumatoid arthritis, sarcoidosis, multiple sclerosis, psoriasis): the search for initiating agents that trigger the acute inflammatory process.

A second dilemma arises in the attempt to explain the chronicity of these diseases. To explain the initiation of the disease process is one thing; to explain its perpetuation is quite another. Few infections are chronic, and those that are (leprosy, tuberculosis, chronic hepatitis, for example) evoke a host response that plays a large role in the expression of disease (as does, for example, granuloma formation in tuberculosis). The other end of the spectrum might suggest that these series of chronic inflammatory states are reflective of an autoimmune process in which immunoregulatory mechanisms have gone awry and tolerance to self is abrogated.

A common thread in these two dilemmas is the potential role of the host immune system. The histopathology of the inflammatory bowel diseases is quite reminiscent of immunologically mediated disorders: in ulcerative colitis an Arthus reaction (type III) with polymorphonuclear leukocyte infiltration, macrophage activation, edema, and immune complex deposition, and in Crohn's disease a delayed-type hypersensitivity reaction (type IV) with granuloma formation and T-cell and macrophage activation. There is little evidence for a directed immunologic attack in either disease, with the potential exception of an autoantibody directed against an epithelial-cell protein described by Das. Recent data suggest that complement activation and deposition does occur in a pattern consistent with the expression of the 40 kd autoantigen, so that, conceivably, complement-mediated inflammation may result.

Still, the important question remains: What is driving the initial response, and why don't conventional regulatory pathways suppress the ongoing inflammation? The answer to that question may relate to defining the normal mechanisms of immune regulation in the gastrointestinal tract. What has become abundantly clear over the past decade is that the immune system in the gut does not follow conventional rules. There are unique populations of cells, such as intraepithelial lymphocytes, whose function has not been defined, although clearly, because they sit at the interface of the internal and external environment, they must have some key role in maintaining homeostasis. There is also immunologic nonresponsiveness, epitomized by oral tolerance, the antigen-specific suppression of an immune response that follows oral feeding. That oral tolerance exists in

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humans has recently been confirmed; whether it is altered or exists in the inflammatory bowel diseases remains to be determined.

So where do the regulatory mechanisms in the mucosal immune system exist? Recent data from several laboratories suggest that intestinal epithelial cells (IEC) may play a dual role in mucosal immune responses: as a transporter of IgA from the lamina propria to the lumen, and as a major antigen-presenting cell. IEC have been shown to express products of the major histocompatibility locus (class II antigens), which present small antigenic peptides to antigen receptors on T cells (resulting in T-cell activation). The IEC, though, are in a unique environment. Many antigens that travel through the stomach and small intestine are "processed" by intestinal enzymes and acid. The requirement for processing by IEC may be limited, and class II molecules may bind luminal peptides and transport them to the basolateral surface, where interaction with T cells (through their antigen receptors) can ensue. Although this preprocessing pathway is advantageous, clearly IEC are capable of taking up macromolecules and processing them into immunogenic peptides in their own right.

Thus the IEC can serve as an effective immunoregulatory or antigen-presenting cell. The unique feature here comes in the type of T cell activated in this interaction. In contrast to conventional antigen-presenting cells (macrophages, B cells, dendritic cells), where helper ($CD4^+$) T cells proliferate, normal epithelial cells selectively activate suppressor T cells. The explanation for this dichotomy is a current focus of investigation, but one of the products of such studies has been the finding that IEC derived from patients with IBD fail to activate suppressor cells, but rather possess many features of conventional antigen-presenting cells, including $CD4^+$ T-cell activation, and enhanced antigen uptake and processing.

The consequences are immediately clear. Activation of $CD4^+$ helper T cells results in the secretion of cytokines which have far-reaching effects in and outside the immune system. The failure to stimulate suppressor cells eliminates the ability of the mucosal immune system to shut itself off, setting up a vicious cycle of antigen entry, immune activation, cytokine secretion, and chronic inflammation.

Several recent studies support this model of inflammatory bowel disease pathogenesis. Two types of T helper cells, Th_1 and Th_2, which secrete distinct profiles of cytokines, have been identified in the mouse and more recently in humans. Th_1 cells secrete IL2 and γ-IFN and are thought to be involved in cell-mediated immune responses or delayed-type hypersensitivity reactions. Th_2 cells secrete IL-4, IL-5, and IL-6, cytokines which promote antibody secretion. Using highly sensitive techniques, investigators have shown that a Th_1 profile of cytokines exists in mucosal biopsies from patients with Crohn's disease (potentially supporting granuloma formation and macrophage and T-cell activation), whereas a Th_2 profile of cytokines exists in ulcerative colitis—more an antibody-mediated histologic picture. Although these observations are tantalizing, the mechanism of this selective activation of Th subsets remains to be determined. Clearly some consideration of genetic predisposition (genetic) resulting in immune dysregulation (immunologic) following exposure to multiple antigens (environment) would satisfy many investigators.

Regardless of what the final answers to these issues turn out to be, these newer areas of investigation have already opened new vistas for therapeutic intervention. Utilization of combinations of agents which can modulate initiating, secondary, and tertiary effects of immune activation may promote rapid recoveries and long-term stabilization of the clinical course in these diseases.

Evolution of the Controlled Clinical Trial

John E. Lennard-Jones, MD, FRCP, FRCS

Historical

The first recorded controlled trial of a treatment was undertaken by a naval surgeon, James Lind, in 1746. Scurvy was rife among seamen at that time because of their poor diet. Lind recognized that the effect of a treatment can be assessed only by planned comparison with other measures. Without such a comparison one does not know if any apparent effect is actually due to the natural history of the illness or is an unusual result of chance. He therefore observed six pairs of sailors, each pair given a different regimen, including a pair given sea water and a pair given two oranges and a lemon daily for 6 days. Those given the citrus fruit recovered with remarkable speed, and the result was clearly better than with the other five regimens. Lind reported these results in 1753 (1) and gradually, as the idea of giving fruit and vegetables gained ground, scurvy ceased to be the scourge of seamen on long voyages.

It was to be exactly two hundred years before the next landmark occurred. In 1946 the British Medical Research Council set up a trial committee of 15 members to test the newly discovered streptomycin in the treatment of tuberculosis. Among its members was Professor (later Sir) Austin Bradford Hill, who was to become a major proponent of the randomized controlled clinical trial (2). This first trial was a model of its kind. A selected group of young patients with bilateral acute progressive pulmonary tuberculosis was randomized into a group treated with conventional bed rest and another treated in the same way but with the addition of streptomycin.

The results, published in 1948 (3), showed that the mortality was less and the radiological improvement greater among those given the antibiotic, but results were best in the first three months of treatment, attributed to the fact that development of drug resistance was noted in the laboratory, often during the second month. Over the next few years the tuberculosis trial group tested combination therapies using streptomycin, and the newly developed INAH and PAS. By 1955, the results of these trials had established the principles of drug treatment of tuberculosis followed ever since.

The controlled trial was introduced into gastroenterology by Truelove and Witts, who in 1954 began their controlled trial of cortisone in active ulcerative colitis (4). The trial fulfilled most of the criteria required of a modern trial. It asked a single clinically important question. The type of disease, namely patients expected to be admitted to hospital for at least 6 weeks, was defined. These patients were randomized into those receiving active or dummy tablets; both patients and doctors were blind to the treatment given. The two groups were stratified into patients with a first attack or relapse of disease. Outcome measures were defined in advance, and these measures were assessed in the short term at 6 weeks and in the longer term at 9 months and two years. Lastly, the results were assessed to determine the probability that the results observed might be due to chance.

Truelove and Witts went on to compare the effects of cortisone and corticotropin, a question taken up again by the group at The Mount Sinai Hospital in their useful comparison of hydrocortisone and corticotropin, both given intravenously, for the treatment of acute ulcerative colitis (5).

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Trial Design

The commonest trial design remains the comparison of two groups treated prospectively. The cross-over design is only appropriate when a symptom is persistent over a relatively long period; it should respond rapidly to an active treatment and recur rapidly when the treatment is stopped without a carry-over effect from one period to the next. For these reasons it is a design of limited usefulness, though it is an attractive concept. The trial of 6-mercaptopurine in Crohn's disease reported from Mount Sinai and Lenox Hill Hospitals (6) was designed in this way and illustrates the difficulties of this design. Only 39 of the patients were crossed over; of the 33 who did not cross over, 22 refused to do so because they were well on the first treatment.

A variant on this trial is the so-called N = 1 design, in which repeated comparisons of two treatments are made in one patient under blinded conditions and in random order (7).

A sophistication of the usual comparison of two treatments (A and B) is a factorial design. A double dummy (a and b) is used, and the patients are divided into four groups, one of which takes both test treatments (A and B), each of two groups takes one test treatment—either (A and b) or (a and B)—with a dummy identical in appearance with the other treatment, and the fourth group takes both dummies (a and b). Thus each test treatment can be compared against placebo, the test treatments can be compared with one another, and a combination of both treatments can be compared with either alone or with the control group taking placebo. It is an elegant design which economizes in patient numbers and gives maximal information, including the possible additive effects of two different treatments.

The sequential trial is an interesting design which aims to give a significant comparison between two treatments with small numbers or indicate when a significant difference is unlikely to be observed. Patients are treated in pairs, one given one of the two test treatments and the other the alternative. If one patient improves more than the other, a diagonal is drawn on the graph, upward if A is better than B or downward for the converse (**Fig. 1**). If the results for the pair are equal, the result is regarded as "tied" and no score is recorded. If the resulting line on the graph hits one of the boundaries, it indicates a significant advantage for one member of the pair. If the line emerges on the right without crossing a boundary, no significant difference is likely to be gained by continuing.

In one such trial, in which hydrocortisone retention enemas were tested against a placebo in the treatment of distal active ulcerative colitis, a significant result at the $P = 0.05$ level (Fig. 1) was obtained after treatment of only six pairs of patients (8).

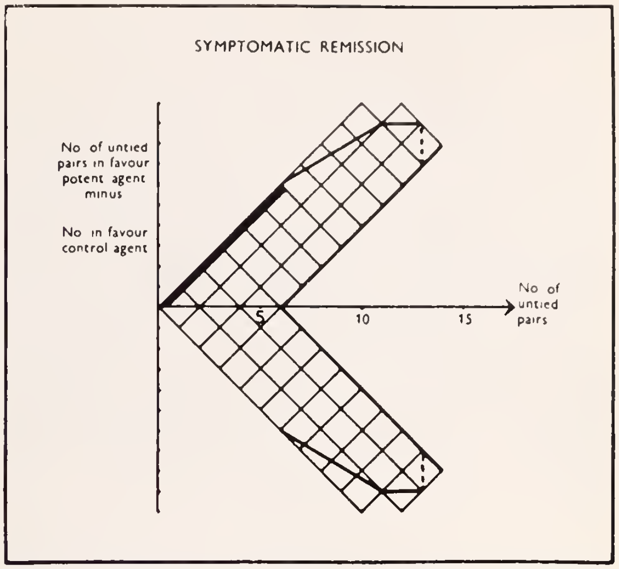

Fig. 1. Example of a sequential trial. In six successive pairs of patients, improvement was greater with hydrocortisone enemas than with placebo in the treatment of active ulcerative colitis. When plotted on the graph (thick line) this result intercepts a boundary showing that the result is significant at the $P < 0.05$ level. *Reproduced with permission* of the author and publisher (ref. 8).

The withdrawal trial is a particularly sensitive design for use when a drug maintains a disease in remission. In this type of trial, patients who are well while taking the drug agree to random substitution of a dummy tablet for the test

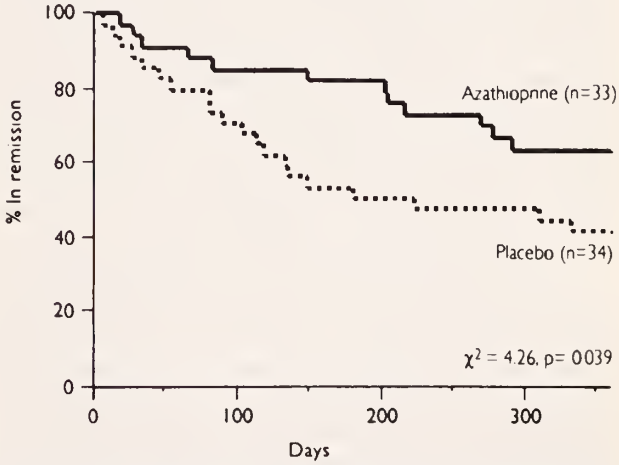

Fig. 2. Example of a withdrawal trial in 67 patients with ulcerative colitis who were in remission while taking azathioprine. When a placebo was substituted in half the patients, the relapse rate was significantly greater over one year in the group taking placebo than in those who continued to take azathioprine. *Reproduced with permission* of the authors and publisher (ref. 9).

medication in half the group, and the time to relapse is noted among those who continue the drug and those who stop it. Fig. 2 is an example of such a trial among patients with ulcerative colitis whose disease was in remission while taking azathioprine. The relapse rate was greater among those who stopped the drug than among those who continued it (9). Previously a therapeutic effect of azathioprine in ulcerative colitis had been in doubt. The reason that this type of trial is such a sensitive test is that patients who do not apparently respond to the drug or those who cannot take it because of side-effects have been excluded, leaving only apparent responders in the test group.

Trial Size

The obvious truth can first be stated: a large difference between two treatments can be detected by a small trial, detection of a small difference requires larger numbers.

At the outset it is important to define what is regarded as a clinically important difference, because this defines the size of trial required. The number of patients in the two treatment groups is determined by the uncertainty inherent in studying a relatively small sample out of a theoretical large total population. Two errors can be conceived. First, a difference may be observed and regarded as real when in fact there is no difference. This is the type 1 error. It is defined by the conventional test of significance, which is based on the null hypothesis that there is in fact no difference. The test of significance estimates the proportion of trials of the same size in which the observed deviation from zero would be found. Thus, if P is calculated to be 0.05, the difference might be observed in 1 in 20 trials, presuming that there is in fact no real difference. The null hypothesis is thus possible but improbable. Repeated testing among subgroups in a single trial may yield a "significant" result in one of 20 tests, a fallacy to be avoided by defining in advance one or a few hypotheses to be tested (10).

The type II error starts from a different premise. It assumes that there may be a real difference between the treatments and estimates the probability that this difference would be missed. The likelihood of missing a difference depends on its magnitude, the numbers in the trial, and the degree of significance demanded of a positive result. The power of a trial is the probability that a difference will not be missed. Thus a power of 0.9 means that the clinically useful difference defined in the trial protocol is likely to be detected in 9 out of 10 trials.

In modern trials it is essential that the trial size be determined at the outset, and convenient tables are available into which may be entered the likely control value and the difference from control regarded as clinically important, the degree of significance which would be accepted as demonstrating the probability that such a difference exists, and the proportion of trials which would detect such a difference. The table then shows the number of patients in each test group necessary to fulfill these conditions.

If trial size is not defined in the protocol, when the results are published, the reader does not know if numbers were arbitrary and depended on the easily available number of cases, if the trial failed to achieve the numbers planned, or if the trial was stopped at a particular point because significance was achieved (10).

If a result is simply reported as "significant" or "not significant," the reader has no concept of the magnitude of the difference observed or the possibility that a real difference exists but was not detected. It is therefore becoming increasingly common to state the mean difference between two treatments and the 95% confidence limits within which the true mean for an infinite population is expected to lie (11, 12).

Thomas Chalmers and his colleagues, working at Mount Sinai Medical Center and at the University of North Carolina, drew vivid attention to this problem in 1978. They analyzed 71 controlled trials from peer-reviewed journals such as the *New England Journal of Medicine,* the *Journal of the American Medical Association,* and the *Lancet,* which had reported "no difference" between two treatments (13). It became apparent that a number of the trials showed a mean difference which may well have differed from zero, though the result was "not significant" because the confidence limits overlapped the zero position. Among these trials only one third were large enough to detect a difference of 50% from the control value in 9 out of 10 trials; the trials were thus too small and real differences were possibly being missed. If trials have to be larger they often have to be multicenter. This necessarily increases patient variability and observer variation. The result is reduced sensitivity but wider applicability of the trial result.

The question of applicability of trial results is an important one. A trial report should state what proportion of all eligible patients were included. Studies suggest that it is necessary to screen about twice as many eligible patients as are actually recruited (14). The results of any trial are only applicable to patients defined by the eligibility criteria. It is therefore also important to know what proportion of the total population of patients is represented by those eligible for the trial.

Outcome Measures

No trial can succeed unless clear outcomes are defined. These can be subjective and rely on the judgment of patients or clinicians. Ideally one needs objective measures which are subject to minimal bias, such as fever, or no bias, such as mortality. In practice many apparently objective criteria—such as healing of ulcers—depend on observer judgment. Intermediate types of outcome are numerical indices, often a mathematical expression of a consensus opinion, such as the Crohn's Disease Activity Index, which is made up of symptoms, signs, a laboratory value, and use of symptomatic treatment. In my view, such indices may give a misleading sense of objectivity, and a study has also shown that clinicians are bad at calculating them (15).

There is much to be said for the therapeutic goals devised by Daniel Present and his colleagues for the trial of 6M-P in Crohn's disease (6). Each goal expresses a real clinical objective which can be expressed as a change from zero, either improvement or deterioration on an arbitrary ordinal scale. The resulting figures can be presented as a mean, to give an overall change with time, or as the values at the end of the trial. In expressing the results it is important to define the degree of clinical improvement, which may vary between slight (+1) and complete (+3) achievement of the goal, and not only its statistical significance.

Ethics

The ethics of controlled trials present major problems. When is it ethical to use a placebo? If an active treatment is available, should the new treatment be compared with it? I have recently been involved with this problem in a trial of a fluorinated steroid with low bioavailability against prednisolone, both given by mouth in the treatment of chronic active Crohn's disease. The new steroid proved to be less effective than prednisolone but, because there was no placebo group, we do not know if the drug is active or not (16). Since it is free of side effects, this remains an important question. It is for this reason that the Food and Drug Administration has rightly encouraged placebo-controlled trials of new drugs. There is no easy answer to this real difficulty, but clearly trials should include an untreated group whenever possible.

This raises the matter of informed patient consent. Doctors are used to dealing with uncertainty, but patients are not. If the outcome of a trial was known there would be no point in conducting it. Patients therefore have to understand the uncertainty inherent in the proposed trial before they can give informed consent. This is difficult because patients want their doctors to know what is best for them. The principle of uncertainty requires a change in the attitudes of both doctors and patients. Doctors need to recognize their fallibility and patients need to recognize that the motives of the doctor are good but that there is uncertainty in the outcome of every recommendation.

Clearly, the safety of the patient is paramount in any projected trial. There must be a reasonable expectation that the new treatment to be tested will be safe. Pharmaceutical companies are now often prepared to compensate patients financially for any unexpected adverse event due to the treatment when it is given within the protocol of a trial initiated by the company (17).

Collaboration in Trials

Collaboration with Patients. The developing relationship between patients and doctors requires a much greater participation of patients within the design and conduct of controlled trials than hitherto. This matter has been brought to the fore during trials of potential new drugs for HIV (18). Patients have felt that they might be denied a possible active treatment for a disease which is at present incurable if they enter a placebo-controlled trial. Patient associations are now becoming involved in the understanding and design of trials so that their members know that their interests and welfare are truly being considered. Issues of quality of life, rather than medical indices of improvement, are now high on the agenda of committees planning drug trials. It is to be hoped that this involvement of patients in clinical trials will become commonplace in many chronic diseases, including inflammatory bowel disease.

Collaboration with Industry. A major factor in most trials nowadays is collaboration with the pharmaceutical industry. Drug regulatory authorities control the introduction of new drugs or changed indications for old drugs. The FDA and equivalent bodies in other countries base their decision on the efficacy and safety of drugs. So that their decisions are based on reliable informa-

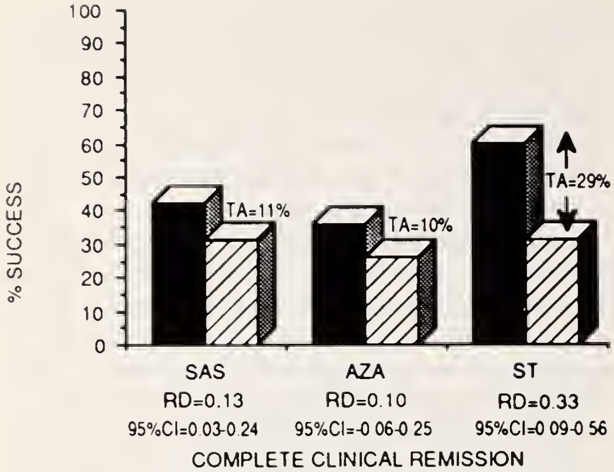

Fig. 3. Results of a meta-analysis of controlled trials of single drug treatments (black bars) in active Crohn's disease. The placebo response (diagonal bars) was about 30%. Sulfasalazine (SAS) and azathioprine (AZA) showed a modest and significant therapeutic advantage of about 10%. Steroids (ST) showed the greatest therapeutic advantage. *Reproduced with permission* of the authors and publisher (ref. 21).

tion, they have issued "Guidelines for Good Clinical Practice" in drug trials. Doctors have to deal with large organizations, there is much extra administrative work, and they have to accept supervision by external monitors.

Almost gone are the days of clinical independence and close personal involvement in a small trial. All concerned have to recognize the economic problems facing a drug firm in the development and clinical assessment of a new drug. Financial rewards may be offered to those undertaking clinical trials which are subject to their own ethical constraints.

Elsewhere, I and others have pointed out the considerable information which can be gained from small clinical trials using confidence intervals in initial dose-ranging trials (19). Such studies are to be encouraged before launching a multicenter trial with its complex organization and large financial outlay.

Controlled Trials Define Effective Treatments

All over the world, health costs are tending to rise out of control. Prof. A. L. Cochrane in the United Kingdom enunciated the law that "all treatment must be proved to be effective" (20). Treatment in this context can be interpreted widely to include all types of medical intervention, not only drugs, but surgical procedures, diets, psychological intervention, physiotherapy, and use of hospital beds. He believed that the use of randomized controlled trials should permeate our clinical practice. In gastroenterology, one thinks of the control of gastrointestinal bleeding, screening for colorectal cancer in the general population, and symptomatic treatments for functional disorders.

His dictum implies that our trials should be designed to consider clinically important therapeutic outcomes—do patients feel better, can they function more effectively, do they live longer? How far does intervention by a doctor really help? For example, are regular follow-up consultations useful? We must put our practice under scrutiny. He also believed that it is unethical not to report the results of clinical experiments. There is a bias against publication of trials with a negative result. It is now suggested that all trials should be registered, that systematic reviews should be undertaken, and that meta-analysis is a helpful procedure. The use of standard abstracts would help this process. An information center to coordinate the results of controlled trials, named for Cochrane, has recently been set up for this purpose in England. Computer-based sources of information are being developed in America.

Tribute to Dr. H. Janowitz

Fig. 3 is taken from the most recent study published by Henry Janowitz and his colleagues, a meta-analysis of single drug treatments in Crohn's disease (21). Note the marked placebo response of around 30%, the therapeutic advantage (TA) calculated for 3 drugs, sulfasalazine, azathioprine, and steroids, and the confidence limits of the relative risk value (similar to TA).

What more could one ask of an analysis of this type? In 1992, as throughout his career, Dr. Janowitz has given a lead and influenced world opinion. It is indeed fitting that the Department of Gastroenterology at Mount Sinai should be dedicated to him. I wish Dr. Janowitz, and the Department, the greatest possible success in the future.

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Advances in Knowledge of Inflammatory Bowel Disease at Mount Sinai Medical Center

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Dr. Henry D. Janowitz wrote in his book, *Inflammatory Bowel Disease: A Personal View* (1), "Ever since I met Burrill Crohn, Leon Ginzburg and Gordon Oppenheimer when I came to The Mount Sinai Hospital in New York in 1939, I have had the sense of participating in the exciting accumulation of knowledge of inflammatory bowel disease and to have been at the frontiers of both ignorance and uncertainty as well as increasing knowledge."

I personally have had the same emotions since I came to Mount Sinai in 1961 and as a gastroenterology fellow from 1964 to 1966. I have been the beneficiary of a tradition of academic excellence and have been exposed to world-famous inflammatory bowel disease experts, including Drs. Janowitz, John Garlock, Leon Ginzburg, Richard Marshak, Arthur Aufses, Jr., Albert Lyons, and Burton Korelitz. I have also worked with outstanding contemporaries who are experts in IBD, including David Sachar, Sam Meyers, Irwin Gelernt, Adrian Greenstein, and Lloyd Mayer. This tradition makes discussing knowledge of inflammatory bowel disease generated at Mount Sinai Medical Center a monumental task, since if I were simply to list each paper written at this institution on IBD the list would stretch to encyclopedic proportions. For my retrospective review here, I therefore asked my colleagues to recommend what they thought were the outstanding accomplishments and papers published in inflammatory bowel disease at Mount Sinai. I tabulated the results to see if they agreed with my own personal prejudices, and for the most part they did.

Historical Perspectives. It is interesting to speculate about the origins of knowledge of ulcerative colitis and Crohn's disease. In prior centuries, nonspecific ulcerative colitis was likely confused with infectious colitis. The name "ulcerative colitis" was first used by Sir Samuel Wilks in 1859, and Wilks and Moxan published a classic description of ulcerative colitis in 1875 (2), slightly over 117 years ago. On the other hand, Crohn's disease appears to be a more recently recognized entity. It was not specifically identified by the great pathologists in Europe in the 19th century, although references have been cited as early as 1806. Wilks and Moxan also described acute ileitis with a pathological picture that sounds similar to what we know as Crohn's disease: "We have met with severe local ileitis in the shape of thickening of the whole of the coats, the wall thick with inflammatory lymph found in patches of from 6 inches to 2–3 feet."

A Scottish surgeon, Dalziel, in 1913 described chronic interstitial enteritis (3) in the same terms as classical descriptions of Crohn's disease, but no followup reports were forthcoming. Many advocates of Dalziel, who claim his paper as the first description, blame this loss of recognition of his work on the start of World War I. In the 1920s a paper by Moschkowitz and Wilenski (4), describing nonspecific granulomas of the intestine, and a paper by Moschkowitz entitled "Sarcoidosis of the Colon" detailed what we can retrospectively identify as typical Crohn's ileocolitis or colitis. These studies separated this en-

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tity from tuberculosis, lymphoma, diverticulitis, and other disorders.

Several years later, Drs. Leon Ginzburg and Gordon Oppenheimer, continuing the work of Moschkowitz and Wilenski, utilizing the pathology provided by Dr. A. A. Berg's surgical service, accumulated 12 cases of localized ileitis in the terminal ileum. Dr. Burrill Crohn had two patients with similar disease who also underwent surgery by Dr. A. A. Berg, and the details of these 14 patients were compiled to describe a new entity which was presented at the annual meeting of the American Medical Association. The three authors of this paper called the entity "terminal" ileitis, but according to Dr. Marshak (5), Dr. J. A. Bargen protested that the term was bad since it suggested a fatal illness, and Dr. Crohn agreed to change the name to "regional" ileitis. This paper by Drs. Crohn, Ginzburg, and Oppenheimer (6) is certainly one of the major achievements in inflammatory bowel disease at Mount Sinai.

Prior reports had been made of the same granulomatous process present in the colon, although it was originally thought that the disease stopped at the ileocecal valve. However, Dr. Ralph Colp in 1934 reported a case with ileocecal involvement showing that the disease could cross the valve (7).

Successes have occasionally been tempered by disappointments. A significant one was the failure of otherwise competent pathologists at Mount Sinai to recognize that Crohn's disease could affect the colon; in reports on the surgically resected specimens, they were typically described as regional ileitis and ulcerative colitis. It remained for Lockhart-Mummery and Morson (8) to clearly define, in 1960, the clinical and pathological features of Crohn's or granulomatous colitis. These authors clearly separated this entity from ulcerative colitis. However, to our credit, our radiological colleagues Marshak and Wolf (9) were quick to describe the x-ray features of what was then called granulomatous colitis. In fact, in a paper before Lockhart-Mummery and Morson's report, Marshak, Wolf, and Eliasoph described segmental colitis (10). However, because of the pathological reports noted above, they failed to distinguish segmental Crohn's disease from segmental ulcerative colitis.

Dr. Richard Marshak joined Dr. Crohn's office in 1946 as his radiologist, and Marshak subsequently became Dr. Janowitz's radiologist. He had the opportunity to see thousands of cases of IBD, and he presented a sequential radiographic history of Crohn's disease distinguishing the nonstenotic from the stenotic phase (5).

The tradition of documenting the features of inflammatory bowel disease has been carried on in recent years in endoscopy by one of the true leaders in this field. Dr. Jerome D. Waye, an outstanding teacher, clinician, and educator, has taught many gastroenterologists how to distinguish ulcerative colitis from Crohn's disease as well as other inflammatory colitides (11).

Megacolon. A major achievement among the radiological contributions from Mount Sinai is a paper on toxic dilation of the colon in the course of ulcerative colitis (12) that reported on 19 episodes in 16 patients, stressing the radiographic features of diagnostic and prognostic significance. In a retrospective review there was at least one patient in this group who had Crohn's disease. This was therefore the first description of megacolon in Crohn's disease, but once again, the pathologic report was that of severe ulcerative colitis with diffuse ileitis. The authors describe cecostomy as successful in some patients and anticipated the future blow-hole surgical technique of Turnbull (13).

This basic paper stimulated the interest of Mount Sinai physicians for several decades. Other contributions to knowledge of this particular complication of inflammatory bowel disease include the papers of Meyers and Janowitz (14) on the role of steroids in megacolon and the large series reported by Adrian Greenstein et al. (15) on toxic megacolon in 75 of 1236 IBD patients, a report that summarizes the institution's experience. My group's contribution to the medical management of toxic megacolon (16) demonstrated decompression in all our patients using a comprehensive medical treatment plan plus the new addition of a simple rolling technique which allowed gas to move from the most anterior portion of the colon (transverse) and to be subsequently expelled. The latter technique was discovered serendipitously when a patient of Dr. Janowitz with megacolon rolled on his abdomen to pick up a book that had fallen on the floor and promptly relieved himself of air and stool across the room, and I was—how shall I say it—fortunate enough to walk into the room 15 seconds later; I subsequently received credit for describing the rolling technique.

Surgical Treatment. Crohn's disease achieved great notoriety when President Dwight D. Eisenhower underwent surgery for obstruction in 1956 and Crohn's disease became a household word. There was great debate postoperatively whether the correct surgical procedure had been performed (17); the president had an ileotransverse colostomy in continuity, which was not universally accepted as the preferred surgical procedure. Many of the debated facts were based on reports from the Mount Sinai Hospital on the surgical management of Crohn's disease.

The initial report in 1945 by Garlock and Crohn (18) of 164 cases detailed the results of surgery in the treatment of regional enteritis; this report was updated in 1951 (19). These long-term followups contributed to the debate on the best surgical procedure for this disorder. Dr. Garlock also published a paper relating his experience in the surgical treatment of ulcerative colitis (20). Following in this great surgical tradition of A. A. Berg, Ginzburg, and Garlock is the comprehensive monograph by Arthur Aufses, Jr., "The Surgery of Granulomatous Inflammatory Bowel Disease" (21). Dr. Aufses has published extensively and taught several generations of surgeons in the operating room, at the bedside, and in lecture halls, and he has an extensive bibliography in this field. I make particular mention of Dr. Aufses because I learned from his advice, and now personally recommend, that gastroenterology fellows go into the operating room to see what surgery in these patients entails, since only in this way can they fully understand the clinical and pathological correlations of inflammatory bowel disease. Dr. Aufses has trained many surgeons in technical skills as well as clinical excellence, resulting in outstanding publications (22–23) from a group including Drs. Isidore Kreel, Irwin Gelernt, Joel Bauer, and Barry Salky, and especially Dr. Adrian Greenstein, as well as many others.

Many would agree with me that one of the major contributions in the postoperative management of inflammatory bowel disease arose at The Mount Sinai Hospital. The first reported ileostomy group in the world was started at Mount Sinai about 1950–1951 and is described in the form of a letter to the Journal of the American Medical Association by Dr. Albert Lyons (24). The club was named the QT Alumni, not to suggest that an ostomy had to be kept "on the QT," but rather after ward Q, the male surgical ward, and ward T, the female surgical ward. The club then became The QT New York and, eventually, the Ileostomy Association QT—New York. A colostomy group was also formed, and Dr. Lyons and Dr. George Schreiber arranged an all-day convention, held at the New York Academy of Medicine and attended by doctors and patients representing ostomy groups from the immediate New York area. It was decided at this meeting to try to create a national organization; ultimately the United Ostomy Association came into existence. From small beginnings in the QT Club, incalculable help in medical education and psychological adjustment has been generated for patients and families. This association has enabled patients to return to normal lifestyles and has substantially enhanced quality of life for many. Most observers account it a major contribution.

Natural History. Studies of the natural history of inflammatory bowel disease have produced an enormous array of original papers that have benefited medical care. Recurrent disease has been studied from many aspects. Dr. Burton Korelitz in 1972 refuted the prior literature which stated that after total colectomy and ileostomy for Crohn's disease there was no recurrence in the small bowel. His series (25) noted a 46% recurrence rate which was subsequently confirmed at other major medical centers. Greenstein and Sachar et al. (26) published a major study on reoperation and recurrence in Crohn's disease using both crude and actuarial life-table methods in 160 patients. The authors cited the deficiencies in the prior literature, requesting more rigid definitions of disease. They noted the inexorable tendency of Crohn's ileocolitis to require repeated operations. Subsequently, the same authors have been enthusiastic about reporting the evidence for two clinical forms of Crohn's disease, a perforating and a nonperforating group, and the need for more frequent surgery in the former (27).

A major natural history paper is the study o 700 Mount Sinai patients describing the extraintestinal complications of both Crohn's disease and ulcerative colitis (28). In this classic study, complications were classified as related either to colitis or to the small bowel or as nonspecific. This review is basic reading for any student of inflammatory bowel disease, at any level of education who seeks to understand the mechanisms and pathophysiology of such complications as arthritis, erythema nodosum, pyoderma, gallstones and renal stones.

The process of understanding the natural history of inflammatory bowel disease continues at Mount Sinai in recent papers. To cite some examples: the first case reports on amyloidosis came from the Mount Sinai Departments of Radiology and Pathology, and in 1960 Dr. Lawrence Werther expanded this experience with an outstanding publication (29). In 1992 Greenstein et al published "Amyloidosis and Inflammatory Bowel Disease: A 50-year Experience with 25 Patients" (30), work which now allows for analysis of the clinical patterns of this serious complication.

Urological complications have been high on the natural history list, starting with Ginzburg and Oppenheimer's paper (31). This initial description of urological complications has been followed by papers on ureteral obstruction (32), hydronephrosis (33), and urolithiasis (34).

Clinical Trials. Among several significant therapeutic trials performed at The Mount Sinai Hospital is the study of Sam Meyers and others comparing ACTH and hydrocortisone in the treatment of severe ulcerative colitis (35). The study demonstrated clearly that intravenous ACTH was the drug of choice for severe ulcerative colitis if the patient had not received prior corticosteroids, whereas intravenous hydrocortisone was preferable for those patients already receiving steroid therapy. The long-term followup of these patients also provided valuable data on the effect of steroid therapy on the natural history of the ulcerative colitis.

Sam Meyers also led a group in a double-blind controlled trial using olsalazine in the treatment of ulcerative colitis patients who were intolerant of sulfasalazine (36). This is an often-quoted trial in that we not only showed efficacy for active disease but at the same time demonstrated a dose response with this therapeutic agent. Our trial helped to obtain Food and Drug Administration approval for the first new 5-ASA agent introduced in the United States. Further international studies of olsalazine have confirmed its efficacy, not only in active treatment, but also in prevention of relapses in ulcerative colitis (see, for example, 36A).

A major contribution has been the demonstration of the efficacy of immunosuppressives in the treatment of inflammatory bowel disease. Burt Korelitz, David Sachar, Nathaniel Wisch, Bernard Pasternack, and I reported on a double-blind controlled trial using 6-mercaptopurine in the treatment of Crohn's disease (37). This has been the basis for multiple followup studies, including evidence for the efficacy of this agent in chronic disease, the only controlled trial in the treatment of fistula (38), and providing the evidence and the rationale for the failure of the national cooperative trial, which used azathioprine but stopped the trial prematurely (39).

Finally, the authors in followup have documented the limited toxicity of long-term use of 6-MP in the treatment of inflammatory bowel disease (40). This trial and subsequent studies have resulted in the avoidance of surgery with maintenance of a high quality of life in innumerable patients suffering from inflammatory bowel disease. Throughout the world more and more patients are being treated with these agents.

Work along these lines continues at Mount Sinai; under the leadership of Simon Lichtiger, a double-blind controlled trial has demonstrated the efficacy of cyclosporine in ulcerative colitis (41; see also unpublished data: Lichtiger S, Present DH, Kornbluth A, et al. A placebo controlled double-blind randomized trial of cyclosporine in severe steroid-refractory ulcerative colitis), the first new therapy for this disease in over 35 years.

Cancer and IBD. Leon Ginzburg gave the first description of carcinoma in the small bowel in a patient with Crohn's disease (42), and a subsequent important paper by Adrian Greenstein and David Sachar, the current chief of the Mount Sinai Division of Gastroenterology, (43) reported on the risks of cancer in ulcerative colitis and the factors determining risk in 267 patients. The same group has reported on the increased risk of extraintestinal cancers in inflammatory bowel disease patients (44).

Basic Science. Although Mount Sinai has a rich clinical tradition, basic science is not ignored, especially with the addition of Lloyd Mayer to our faculty. Dr. Mayer is considered one of the world leaders on basic immunologic defects in patients with inflammatory bowel disease. His data, published in 1990 in the *Journal of Clinical Investigation* (45), suggests an intrinsic defect in epithelial cells taken from IBD patients, resulting in the inability to normally stimulate suppressor T cells.

Legacy of Henry D. Janowitz. Among Henry D. Janowitz's recent interests are his return to the natural history of Crohn's disease, performing a critical review of the placebo response in multiple trials (46), as a recent meta-analysis, conducted with three young fellows, of the efficacy of drugs currently being used to treat Crohn's disease (47). Nor should we ignore his important paper on the quality of life after surgery for Crohn's disease (48).

A major achievement of Dr. Henry Janowitz is to have been the medical founder, along with two lay founders, Irwin Rosenthal and William Modell, of the Crohn's and Colitis Foundation of America, which began at Mount Sinai as the Foundation for Research in Ileitis. It subsequently became the National Foundation for Ileitis and Colitis and is now called the Crohn's and Colitis Foundation of America. Their initial grant to Mount Sinai for the first year was $25,000, (of which only $20,000 was spent) and it enabled us to launch our immunosuppressive trial as well as several other studies. Now, 25 years later, the Foundation has given $21 million to research, $2.55 million in 1992, including 200 research grants and 156 training awards. Sixty-one percent of Foundation recipients go on to receive National Institutes of Health funding. In addition, 1700 physicians are now members of the organization, as are over 100,000 patients and donors.

What a legacy from this remarkable man. In much of what I have described as Mount Sinai Medical Center accomplishments in inflammatory bowel disease, Dr. Henry D. Janowitz has played a major role: as a basic physiologist, a collaborator, a teacher, a mentor, and, finally, cofounder of a major foundation dedicated to supporting research and education internationally. The name of this outstanding physician and gentleman is a fitting endowment for the Dr. Henry D. Janowitz Division of Gastroenterology.

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Reminiscences of Henry D. Janowitz

A journey of learning, accomplishment and fulfillment—Henry D. Janowitz 1959–1963: I arrived at The Mount Sinai Hospital on June 21, 1959, shortly after my discharge from the Israeli Air Forces. This was my first trip abroad and needless to say, I was overwhelmed by my impressions of New York and of The Mount Sinai Hospital. After two and a half years of active service as a flight surgeon in the Israeli Air Forces, a position considered to be most stressful and requiring alertness, agility, and ability for quick and rational response, I could hardly believe the pace of activity and sense of urgency everywhere around me in the hospital. It was a beehive of research and clinical activities, and I was most impressed and flattered by the opportunity of meeting a number of famous personalities whom I knew only from their publications.

I was introduced to Henry in one of the hospital elevators by Dr. David Adlersberg, who was responsible for my coming to America and with whom I was supposed to do research on the differences in the metabolism of lipid emulsions administered intravenously or after absorption by the intestine. Henry was quick to point out that anything that has to do with the intestine should be of interest to him, that I would be more than welcome to join the activities of his group, and that I should feel free to discuss questions or problems related to my research. At that time neither Henry nor I realized the importance of this statement.

Not long after this conversation, Dr. Adlersberg succumbed to a massive heart attack, and as a consequence my research project and my future at The Mount Sinai Hospital became questionable. By a cruel stroke of fortune, I found myself without financial support, laboratory facilities, research supervisor, or mentor. The only one that I could think of turning to was Henry, and his response to my predicament determined my destiny and reshaped my future.

Henry made sure that I could continue my research, provided advice and leadership, and also allowed me to participate in the clinical activities of his department and obtain my clinical training in gastroenterology. I was given a corner in the laboratories of Dr. Harry Sobotka, the director of Clinical Biochemistry, who had done pioneering work on the biochemistry of bile salts. Dr. Sobotka also gave me the key of a not-well-known storage area several floors under the basement, literally in the "guts" of the hospital. Here I found all sorts of glassware and incubation baths and a micropipette which I used in my work on free fatty acids. In this area were also stored some of the personal possessions of renowned refugee scientists from Germany. Here I found the kymograph used by Dr. Otto Loewi in the discovery of acetylcholine, a discovery for which he was awarded the Nobel Prize in 1936. Here was also stored a harpsichord which belonged to Dr. Sobotka's wife, herself an accomplished concert performer, on which I took the liberty of playing during some of the lonely hours away from the laboratory bench or ward duties.

The next spring I had the privilege of having one of my abstracts selected for presentation at the meetings in Atlantic City. I remember the endless rehearsals along the Garden State Parkway of my presentation with Henry's tenacious coaching on voice, intonation, body posture, and control of the motions and position of my arms and hands. It was indeed a miracle that we arrived safely, because I was also doing the driving. Henry insisted on my rehearsing the answers to a number of possible questions from the audience and—typical of Henry's foresight—most of these questions were indeed asked after my presentation. The presentation was a success, and what I learned from Henry during our drive to the conference proved to be of immeasurable help in many more presentations in the years to come. This was a journey of learning.

A few years later, when I accumulated a reasonable list of publications, Henry nominated me for membership to the prestigious American Society for Clinical Investigation. Dr. Jules Hirsh of The Rockefeller University, New York, and Dr. Marvin Sleisenger of the University of California School of Medicine, San Francisco, seconded the nomination. My acceptance as a member of the "Young Turks" signified the recognition of my research accomplishments and once again reinforced for me the immeasurable help and guidance so generously provided by Henry. This was a journey of accomplishment.

Finally, the day came when I had to start the journey on my own. I had finished my clinical training while carrying out active and productive research, and it was time for me to move on. Although Henry was very interested in having me join the Division of Gastroenterology at The Mount Sinai Hospital, he was understanding of my needs for my professional future and was not only encouraging and supportive, but also actively promoted my search for a suitable academic position. I was appointed chairman of the Division of Gastroenterology at McGill University, and Director of Gastroenterology at the Royal Victoria Hospital, Montreal. This was a journey of fulfillment.

Looking back, I can only wonder what might have happened if Henry had not been there when I was in greatest need of help, advice, and guidance. I am glad that Henry was there on that fateful elevator ride, for outside of my immediate family there is no one whom I respect more or to whom I owe so much. It has been a most enjoyable journey, and I hope that we will have many more and longer distances to travel together.

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The British Medical Research Council awarded me an **Eli Lilly Travelling Fellowship** to spend 1961–62 in a gastroenterology department in the United States. I took advice, was told that there were three distinguished gastroenterological centers in America, and after discreet enquiries applied to Dr. Janowitz, the newly appointed chief of gastroenterology at The Mount Sinai Hospital.

He accepted me provisionally by correspondence but asked to interview me when he and Dr. David Dreiling came to London in June 1961 for the CIBA Foundation Symposium on the Exocrine Pancreas. I told them what I had been doing—in my research 1959–1961 in a medicine-gastroenterology residency at the Middlesex Hospital, London, I measured acid output with Kay's augmented histamine test—and they asked what I would like to do in my year with them. Did I know anything about pancreatic secretion? No, I said. Their response: Then you'll learn about it when you come!

Maximal Outputs of Gastric Acid and Pancreatic Bicarbonate. In London I had devised a new methodology for calculating maximal acid output. What I called peak acid output (PAO) was the mean of the two highest consecutive collection fractions after a single parenteral dose of agonist (1). This PAO was highly repeatable and clearly represented parietal cell mass. I propounded the still-current threshold model of duodenal ulcer disease (DU) in which DU was found only with PAO more than 15 mmol/h or 10^9 parietal cells (2).

In New York I joined the late Claude Perrier of Geneva in trying to establish a maximal alkaline output of the dog pancreas analogous to maximal acid output of the stomach. Our attempt was feasible and safe only because of the commercial availability of the more purified Jorpes-Mutt Vitrum secretin. By cannulating the major pancreatic duct in dogs with long-term Thomas fistulas we achieved maximum bicarbonate output with either single intravenous injections or continuous intravenous infusions, and we could produce inhibition by supramaximal doses (3).

We showed that the dog pancreas could secrete about one third as much alkali, milliequivalent per milliequivalent, as its stomach could secrete acid (4). There was, however, no significant correlation between maximum bicarbonate output and maximum acid output (4). Nevertheless, there was a highly significant correlation between maximum bicarbonate output and weight of pancreas (4), a project continued by Jack Hansky and Oswaldo Tiscornia (5). Later, in London with Gutierrez I was able to use our near maximal peak bicarbonate output after even purer GIH secretin in humans with and without chronic pancreatitis and compare peak bicarbonate output with submaximal bicarbonate output to Boots secretin.

Although in the dog, Perrier and I (4) found no significant correlation between maximum bicarbonate and acid outputs, I was able with Gutierrez to find a correlation in humans. Bicarbonate secretory capacity in patients with DU was normal and comparable to gastric acid secretory capacity (7). It was the basal bicarbonate output of the duodenal aspirate in patients with DU which was only half that of control subjects and which led to decreased neutralization of gastric acid in the duodenum. However, I have rather abandoned the pancreas in the last 20 years and confined myself to the stomach.

I was also trained in David Dreiling's Experimental Surgery Laboratory in Allan Kark's Department of Surgery. Lewis Burrows, Walter Wildstein, and I (8) studied the maximum histamine response (MHR) of denervated fundic pouches in dogs, and found the most repeatable measurement was my PAO with a mean coefficient of variation of only 12%. We used this MHR by PAO methodology to look at the effect of drugs such as Mecholyl, secretin, and insulin. Mecholyl could potentiate submaximal histamine acid output to a PAO even greater than MHR (8).

Paradoxically there were increases of a third to one half of MHR of Heidenhain pouches after transthoracic vagotomy (9). However after antrectomy there were marked decreases in MHR; vagotomy after antrectomy now inhibited instead of augmenting acid. We interpreted this paradoxical acid stimulation by vagotomy as an augmentation of gastrin release from diminished fundal acid output, which had a bigger effect than the decrease of gastrin release through antral denervation. We could but speculate, because gastrin could not then be measured.

Our group also devised a protocol for measuring, both before and after acid lowering operations, 12-hour overnight acid output, hourly pH, and basal and peak acid outputs after an augmented histamine test (10). This protocol was to be used in a policy for selective surgery for DU, but I left before this began.

The Spirit of Sinai. After four years at Oxford, two years in the Army, and seven years at the Middlesex Hospital in London, it was profoundly stimulating to be in a different country, a different city, and a different biomedical milieu. Just as American cornflakes came in three sizes, large, giant, and jumbo, so also did Sinai laboratory, clinical services, and staffing seem generous beyond my experience, if hardly surprising, the United States having twice the British GNP and spending twice the percentage of GNP on health than did the UK.

Sinai residents and fellows had qualified after eight years in college and medical school, compared with our five or six, but then worked hard and fast to become independent specialists within five or six years, compared with our ten or twelve. I spent two of my twelve months in the United States visiting many of its great medical centers and found some even more lavish, but none more dynamic, than Sinai.

Sinai had a demonic pace, as each trainee strived to acquire clinical and technical skills on the one hand and then in research time to achieve measurable success—"think it, do it, publish it." Organizationally I have tried to emulate that weekly timetable of gastrointestinal meetings both alone and with radiologists, histopathologists, and surgeons. I still vividly recall sessions with Franklin Hollander, Richard Marshak, Fenton Schaffner, and Hans Popper, as well as Gutman's Medical Grand Rounds.

The only disappointments were a double dose of parochialism. Nobody at Sinai asked me anything about the British National Health Service. When I returned to London nobody wanted to hear anything about the health-care scene in the United States.

Henry Janowitz. What were the secrets of Henry Janowitz's achievements? First of course his intellect, honed by generations of study. Second, he had not only read everything, but remembered only what was relevant. Third, agility: to concentrate totally on the scientific or clinical problem at hand, to comment positively (or negatively) with suggestions of where to go next (or to stop a project clearly going up a blind alley): he could then put that problem out of his mind and move onto the next resident or fellow. Fourth, pragmatism: he had a shrewd idea of the assets and deficits of those in his own and other units, and he also knew how to live with them: "any big unit should be able to tolerate at least one bastard." Finally, conjugality, with the warm ambience and hospitality at his home with Addie—to whom, and to Henry, in gratitude of both my year at Sinai and our subsequent friendship, I wish not Happy Retirement but Happy Continued Productivity.

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A tribute to Henry D. Janowitz from his most distant metastasis: I joined the Division of Gastroenterology at The Mount Sinai Hospital in July, 1962, as a research fellow. I had come for a year's training, after spending a year at the Central Middlesex Hospital in London with Francis Avery Jones. Luminal gastroenterology at Mount Sinai in those years was noted for focusing on two areas: pancreatic pathophysiology and inflammatory bowel disease. Henry Janowitz decided that I was made for the pancreas, and I spent the ensuing 12 months alternating between dogs equipped with Thomas cannulae in the Atran laboratory and intubating patients with Dreiling tubes for secretin tests. Henry Janowitz and David Dreiling took me under their wings and stimulated my first love in gastroenterology—the pancreas. The year was very productive in terms of publications, research work done, and techniques learnt.

What were some of the memories from that year? Tutorials with and presentations to Frank Hollander on gastric and pancreatic physiology; Friday lunch meetings with David Dreiling and the dog team, where I was introduced to pastrami on rye and Dr. Pepper's; Grand Rounds under the stern chairmanship of Alex Gutman; learning about serotonin from Dick Warner and the esophagus from Bernard Cohen; doing rounds with Henry Janowitz, Nat Cohen, Larry Werther, Jeff Friedman, Al Gelb, Art Lindner; and sharing knowledge with Jesse Berkowitz, Richie Rosenberg, Jared Kniffen, Jerome Waye, Jacques Kessler, Hugh Baron, Oswaldo Tiscornia, Mort Davidson, and Gene Aronow. I also recall my nervous presentation of some aspects of pancreatic physiology at the Federation meeting in Atlantic City where Mort Grossman made incisive comments that have lasted for 30 years. I particularly treasure memories of the fantastic hospitality shown by all at Mount Sinai, but especially by Eileen and Nat Cohen, Addie and Henry Janowitz, and Muriel and David Dreiling, who made life in Manhattan very exciting for Paula and me and our two small children.

If one examines the names of the people who were at Mount Sinai in 1962–1963, one finds that they have all made significant contributions to gastroenterology over the years and have paved the way to make the Division of Gastroenterology at Mount Sinai one of the best in the United States.

Three people most influenced my career in gastroenterology—Sir Francis Avery Jones, Henry Janowitz, and Mort Grossman. Both Grossman and Janowitz worked with Ivy in Chicago, and both were considered brilliant gastrointestinal physiologists, but they then proceeded on divergent paths—Grossman to a full-time physiologic research career and Janowitz to a mixture of patient care and research.

Henry Janowitz did both activities exceptionally well. He molded a strong department with excellent clinical ramifications together with a research team that produced world-class research and publications in "good" journals. His program attracted applicants from all of the United States, and the excellence of his program also influenced a number of foreigners to apply to work with him at Mount Sinai. Thirty years ago, the number of training posts in the country was not as vast as it is now, but one of the best was at Mount Sinai. I was fortunate that Henry had a position available when I was ready to come to the United States and that there was such a vast array of clinical material to learn from. The year proved very fruitful in terms of research papers published—there were seven or eight—and techniques mastered. It was, of course, not only luminal gastroenterology that was so well taught, but also liver disease with Fenton Schaffner and Hans Popper.

My year at Mount Sinai with Henry Janowitz was of such moment that it influenced my decision to take up a full-time academic post in Melbourne, Australia, where I could try to emulate Henry—there was a goodly blend of research, teaching, and patient care. On my return to Australia, I tried to continue my research in basic pancreatic physiology but was unsuccessful with Thomas cannula dogs, so my energies went instead into clinical pancreatic function tests, with development of a maximal test for pancreatic secretion; into esophageal motility; and into radioimmunoassay of the hormone gastrin. My training at Mount Sinai under the expert tutelage of Henry D. Janowitz was the key to my success as a gastroenterologist, researcher, and teacher, and I am very proud when Henry Janowitz refers to me as his "foremost metastasis."

I could conceive of no greater honor than to have a unit named after oneself (whilst still living and active). Although Henry has had many honors bestowed upon him, I am certain he will cherish the present one the most. Henry D. Janowitz—well deserved!

Jack Hansky, M.D.
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In 1968 I had an interview with Henry Janowitz as a requisite to becoming a gastrointestinal fellow. He accepted me and I had to start in July 1969. However, I could not start on time because I was finishing the gastrointestinal residency in Venezuela. I wrote a letter to Henry and he answered, "So if you start a few weeks later, you will win the Nobel Prize a few weeks later." It was my first experience with Henry's sense of humor.

Coming to New York with my wife and two babies was not easy, but Henry Janowitz made sure that I felt at home beginning with my first week in his department. I was treated with friendliness and respect, which at that time was a much-needed sensation.

My two years as a gastrointestinal fellow at Mount Sinai (1969–1971) were exciting and productive. I found a group of hard-working people doing the most varied research, combined with excellent work under Henry's supervision.

After the first month I started to work at the laboratory on the effect of ATPase inhibitors and cyclic AMP on pancreatic secretion. For me, this experience was the most rewarding. I learned how to do research. I remember meeting with Henry at 9 or 10 PM to discuss the results of my work. I had never before had a meeting to discuss ongoing research that late at night. However, Henry was different. He was an extremely hard-working man. He has been a model for me.

At medical rounds Henry was a master. Being an excellent clinician, and a smart one, he allowed and encouraged everybody, including the fellows and young physicians, to give their opinions before he gave his own. Sometimes, during a clinical discussion of a difficult case, one of the young residents—David Sachar—left the room to look for some unusual information on the case in his "computerized" hole-punch card system. I enjoyed these discussions and today, I manage clinical discussions in a style I learned from Henry. I learned endoscopy at Mount Sinai, and I was lucky to have Jerome Waye also learning how to use the Gastrocamera and the new fiberoptic scopes. Also, I had the opportunity to work in the motility laboratory with Bernie Cohen, who taught me esophageal motility and even how to prepare my own esophageal catheter. Since then, I have been a "motility man."

Today, as chief of a gastrointestinal department in a teaching hospital in Caracas, Venezuela, I am sure that my directing style has been influenced by my experience in Henry Janowitz's department.

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As part of my gastroenterology training at the Mount Sinai Medical Center, I was resident to Dr. Henry Janowitz for six months in 1972. I have always felt that it was an honor and a privilege to have held this position. Through his endeavors as a clinician, scientist, and humanist, Dr. Janowitz has had a profound influence on my career.

The most important impact has been in the area of time management. As is the case with most academic physicians, my activities include patient care, teaching, research, and administration, two or more somehow frequently occurring simultaneously. Working with Dr. Janowitz taught me four "rules" that govern most of my time. Two apply to all aspects of my work, and the other two concern clinical practice.

Henry's first rule: Focus. Do only one thing at a time, and do it well. This doesn't mean you must finish one item before beginning another; it simply means don't do two things at the same moment.

His second rule: Be flexible and adaptable. A vignette comes to mind to illustrate this point. One day, we were asked to see a man with Crohn's disease and bacterial overgrowth secondary to an ileal stricture. We were told that the patient was rather compulsive and had requested that only Dr. Janowitz should question him and examine him. When we entered the room, the man was washing his hands. In the course of getting ready to get into bed for the physical, he returned to the sink several times to wash and rewash his hands. As Dr. Janowitz was about to begin the examination of the abdomen, the patient said, "Just a minute. You can only examine my abdomen if you are prepared to follow certain rules! You can start wherever you want, but once you touch me below the belly-button, you are not allowed to touch me above the belly-button again!" This led to a rather unorthodox method of abdominal examination; nevertheless, it was accomplished without discussion or complaint.

Henry's third rule: Take your time. He always took as long as was necessary to get the complete story, so that the correct decision would be made.

His fourth rule: If your patient needs a surgeon doctor, he or she still needs a doctor doctor. This was not meant to say that the surgeon is merely a technician, only that most gastrointestinal problems are codisciplinary. As Dr. Janowitz's resident, I had to report to him from the operating room to let him know if the findings were as expected. If not, then I was the go-between for the discussion, subsequent to which a joint decision was made. I have followed this practice for the past 21 years. My surgeons have come to accept and appreciate my input.

My first 14 years were almost entirely clinical. In the past seven years, Dr. Janowitz's thirst for knowledge through research has had an increasing influence on me. Since becoming head of our division, I have developed an active clinical trials program and have become the codirector of a research laboratory.

In summary, Henry Janowitz has had a pervasive effect on all aspects of my career. I feel that I have followed in his footsteps, though my shoe size will always remain smaller than his.

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We surgeons have known, worked with, been taught by, and admired Henry for almost 40 years. My colleagues and I never cease to be amazed by him. He is a superb physician whose clinical acumen and judgment are brilliant. To us, Henry represents the ultimate gastroenterologist and gastroenterological consultant. It is a rare privilege indeed to have been asked by Dr. David Sachar, chief of the Dr. Henry D. Janowitz Division of Gastroenterology, to represent the Department of Surgery in this tribute to Henry D. Janowitz.

Henry is a man of few words, but always listen carefully to him; you will learn much. He is pragmatic but rarely dogmatic. If you choose to disagree or argue an opposing view, be sure of your facts, because Henry's experience and knowledge are so vast that you will rarely win. By the same token, when you are confronted with a decision on whether or not to operate, Henry's opinion can be all-important. He has the amazing ability to know the therapeutic limitations of both medical and surgical management in any given case.

Henry has published extensively, but to me his book *Inflammatory Bowel Disease—A Personal View,* above all others, contains a treasure trove of helpful information in caring for the patient with IBD. Although Henry is rarely dogmatic, he entitled Chapter 3 "The Nature of the Beast: A Speculative Chapter with Some Dogmatic Comments." But then, in typical Henry Janowitz fashion, the first sentence of the chapter notes that "readers who find speculation unprofitable may want to skip this Chapter and move on." There are multiple quotable quotes in this book. In a discussion of the rarity of appendicitis in Crohn's disease and the occurrence of isolated Crohn's disease of the appendix, Henry notes, "[My] impression must have some validity." He is absolutely on the money when he states: "most medical errors, I believe, are errors of omission. What we do is essentially rational; it is what we do not do that is important." This could well represent the surgeon's as well as the internist's credo.

Those of us who have the current good fortune to be members of the Department of Surgery at Mount Sinai stand on the shoulders of giants. We recognize the enormous debt we owe to Drs. Garlock, Ginzburg, Colp, Klein, Dreiling, Lesnick, Kirschner, Klingenstein, and others for their teachings. Our department is recognized as a major center for gastrointestinal surgery. In having achieved this designation, we are ever mindful of and pay tribute to Henry and his disciples for the role that they have played in our success. Not only has Henry been personally involved in the care of so many of our patients, but he has also been a major contributor to our research endeavors and teaching activities. Henry has been the mentor of almost all of the gastroenterologists who now make up the superb Dr. Henry D. Janowitz Division of Gastroenterology, so ably headed by Dr. David Sachar. They have formed a liaison with us in a spirit of collegiality that is the envy of many academic health centers. Together we have been able to advance medical knowledge, render superb patient care, and provide the finest teaching in the field of gastrointestinal disease.

Henry—we salute you and congratulate you on the occasion of this Festschrift in your honor.

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Twenty-five years ago, Henry D. Janowitz, M.D., listened to the frustration of the families of those who suffered from Crohn's disease and ulcerative colitis and gave them the precious gift of hope. He challenged them to raise funds to develop the first national research program dedicated to ending the scourge of these inflammatory bowel diseases (IBD). In exchange, he promised to lend his prestige to their undertaking and helped establish the Crohn's & Colitis Foundation of America (CCFA). He provided guidance and leadership to this fledgling organization, fostering the growth of IBD research across the United States. Indeed, as much as any single physician, Dr. Janowitz has had the most dramatic influence on research that seeks to find the cause of, and cure for, IBD.

From 1967 to 1975, Dr. Janowitz served as the National Scientific Advisory Chairman for CCFA. During his tenure, he nourished the dreams of scientists and lay persons alike. Painstakingly, he expanded CCFA's research program. From initial projects that sought to define more clearly the clinical aspects of IBD and to establish a basic epidemiological profile of patients, CCFA's research program expanded its scope to include basic research that began to investigate the role of the immune system in IBD and to determine whether or not infectious agents triggered its onset. Reaching out beyond the New York community of researchers, he encouraged scientists at such prestigious institutions as the Johns Hopkins University School of Medicine, the Cleveland Clinic, the University of Chicago, Massachusetts General Hospital, and Cedars-Sinai Medical Center in Los Angeles to focus their studies on IBD. By 1975, CCFA had funded research grants at 21 hospitals in 13 cities, totaling $1,470,433.

When Dr. Janowitz stepped down as the chairman of CCFA's National Scientific Advisory Committee, CCFA was firmly established as a respected presence in the research community. As a testament to his work, one of America's leading clinicians and researchers in the field of IBD accepted the chairmanship of CCFA's National Scientific Advisory Committee. He was Joseph B. Kirsner, M.D., Ph.D., Louis Block Distinguished Service Professor of Medicine at the University of Chicago.

Because of Dr. Janowitz's belief in the ability of research to conquer IBD, his extraordinary talent as a mentor, and his enormous enthusiasm, CCFA is now one of the premier health organizations in America. Since 1967, CCFA has invested more than $19 million in research projects in the United States, Europe, and the Middle East. Its researchers have identified a mouse model, are building a cell-line bank, and are close to identifying the gene markers for Crohn's disease and ulcerative colitis. They also are making exciting headway in their understanding of the role of the immune system. In addition, they have improved medical and surgical treatment of these diseases and sharpened pathologists' diagnostic skills. Their success has engendered greater interest in, and support of, IBD research at the National Institutes of Health. For each of the past three years, the federal government has earmarked $2 million specifically for IBD research.

Hundreds of thousands of people who have Crohn's disease or ulcerative colitis have received educational material and supportive services provided by CCFA. Once a "closet" disease, IBD is now regularly discussed in major newspapers and national magazines and on radio and television talk shows. Celebrities and athletes throughout the United States speak out in behalf of CCFA's research and education programs.

In the mid-sixties, Dr. Janowitz fostered the dream of Irwin Rosenthal, an attorney, and William Modell, a businessman. Together, these three men gave birth to a national organization of dedicated medical and lay volunteers who one day will find a cure for inflammatory bowel diseases.

On behalf of the Crohn's & Colitis Foundation of America and the estimated two million Americans who suffer from the inflammatory bowel diseases, I proudly salute and honor a great physician, researcher, and humanitarian.

Jane W. Present
Chairman of the Board
Crohn's & Colitis Foundation of America, Inc.

Obscure Gastrointestinal Bleeding

Blair Lewis, M.D.

I want to review here the experience at the Mount Sinai Medical Center with gastrointestinal bleeding of obscure origin and explore how many different doors of clinical research have been opened by that experience.

A simple case presentation exemplifies the type of problem I am addressing. A 73-year-old man I saw recently had been bleeding for the last two years. During those two years he received 30 units of transfused blood. He had two small-bowel series, two barium enemas, four upper endoscopies, five colonoscopies, a couple of bleeding scans, an angiogram. He continues to bleed from an unknown site.

Fortunately, the site of bleeding is identified in most patients who have gastrointestinal bleeding. Only an estimated 3%–5% of patients who bleed from a gastrointestinal source have obscure gastrointestinal bleeding—bleeding whose site cannot be found despite routine testing.

Several reasons account for the inability to identify the site of bleeding:

- The bleeding rate may be so slow as to make certain tests, such as bleeding scan or angiogram, unsuccessful at showing extravasation of blood.
- Bleeding can be intermittent; the person may be bleeding in the physician's office, but when that patient gets to the emergency room, he or she has stopped bleeding, and whatever testing for extravasation of blood is performed from then on will be unsuccessful as well.
- The majority of these lesions are vascular ectasias. Endoscopists have learned that these lesions can vasoconstrict right before the physician's eyes, and disappear; a physician may be looking at one one moment and not see it the next. That makes diagnosis difficult.
- Even if a bleeding site is found and treated, by whatever method, the patient may go on to bleed, because the true cause of bleeding has not been discovered. Not everything the physician finds and treats will be the actual cause of blood loss.

Causes

Angiodysplasia. Angiodysplasias have many different names: arteriovenous malformations, vascular ectasias, angiomas, arteriovenous fistulas. Since 1977, when Scott Boley first taught us about these vascular ectasias, our knowledge has increased. Boley originally said that angiodysplasia was a disease of the elderly (patients were over the age of 60); that the lesions most commonly occur in the cecum or the right colon; that the lesions were small (1). He said that they were diagnosed by angiography and not by endoscopy, which we now know is not true; endoscopy does play a major role in diagnosis. Yet the true pathology or pathophysiology of angiodysplasia is still unknown.

We now know certain other factors about angiodysplasias. In addition to a predilection for the elderly, the disease tends to be associated with certain illnesses. Aortic stenosis has been thought to be a factor in the development of angiodysplasia. Recent literature and prospective studies using echocardiography along with endoscopy and angiography have shown that aortic stenosis is not a cause of angiodysplasias and is not a risk factor independent of age (2). We know that renal failure is associated with the development of vascular ectasias, usually in the stomach. This association was established by Zuckerman, who

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showed that when patients with acute upper gastrointestinal bleeding were examined by endoscope, vascular ectasias were found in the majority of those with renal failure, but in only a minority of those without renal failure (3). Other diseases, such as Osler-Weber and von Willebrand's disease, are widely known to be associated with telangiectasias.

How do these angiodysplasias form? Scott Boley formulated a theory about the development of angiodysplasia that is widely accepted, but still debated; it remains a theory (1). Some knowledge of microcirculation in the colon is needed to talk about his theory (**Fig. 1**).

Boley hypothesized that distension of the cecum and the ascending colon leads to chronic intermittent obstruction to venous outflow. If this process continues over many years, the capillary beds (honeycomb complexes) become dilated, whereupon the back pressure could then be fed to the arteriolar side. Finally, the arteriolar side would lose its prearteriolar sphincter, causing in essence an arteriovenous fistula and further dilation of the capillary beds and forming an angiodysplasia, which could then bleed.

Other Causes. Angiodysplasia is not the only cause of obscure bleeding. Among the many other causes are small-bowel tumors and ulcerations of the small intestine (**Table**).

Nonenteroscopic Diagnostic Tests

Small-Bowel Series. A variety of tests are available to help make the diagnosis in these patients. But I must adjure physicians not to forget the basics. I think that we endoscopists have been very good at brainwashing the medical community into thinking that endoscopy is the end answer, and to forget about the basic tests, upper gastrointestinal series and barium enema examinations. For example: a 67-year-old man came to The Mount Sinai Hospital with melena. No abnormalities were detected in an upper intestinal endoscopy or colonoscopy. The treating physicians said, "Blair, why don't you do an enteroscopy to try to figure out where the bleeding is coming from?"

I responded, "Why don't you do a small-bowel series?"

"Well," they said, "the yield of small-bowel series is low."

I said, "Yes, but it's easy to do, it's inexpensive, it's not traumatic for the patient, it's not a lengthy examination." Moreover, it was part of our protocol for doing enteroscopy.

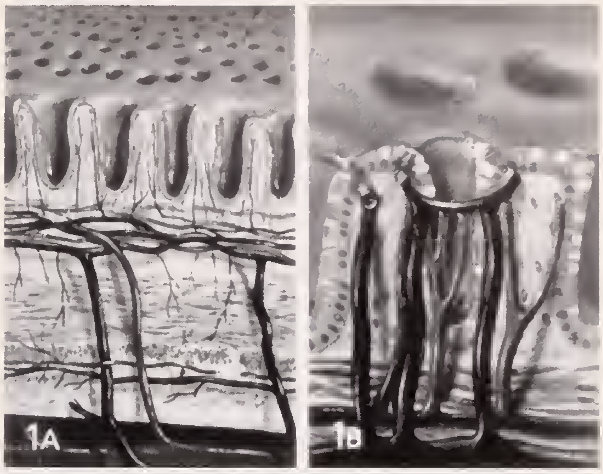


Fig. 1. Colonic crypts are fed by arterioles that come up from the serosal layer and then form circles at the tops of the crypts. These circular capillary beds are called honeycomb complexes. Venules drain down through the muscularis propria and into the veins. *Reproduced* with permission from ref. 1.

So they did a small-bowel series and within the third portion of the duodenum (**Fig. 2**) was an annular lesion, a pancreatic cancer that was growing into the duodenum. That was the cause of bleeding in this patient.

The small bowel has been considered relatively inaccessible in the past, and the development of enteroscopy does allow direct visual inspection of the intestine. Routine upper intestinal endoscopy does not reach the third part of the duodenum; it will reach the second portion, and occasionally the junction of the second and third portions. This case, in which the diagnosis was not, and could not have been, made by routine upper endoscopy, shows how helpful a small-bowel series can be, even though the yield is low. In a recent series of a hundred patients with obscure bleeding, no diagnoses were made with the small-bowel series (4). Still, a small-bowel series should be considered one of the basic diagnostic tests.

TABLE
Causes of Obscure Bleeding

Brisk bleeding	Occult bleeding
Angiodysplasia	Angiodysplasia
Leiomyoma	Adenocarcinoma
Leiomyosarcoma	Lymphoma
Jejunal diverticula	Carcinoid
Crohn's disease	Crohn's disease
Aortoenteric fistula	Zollinger-Ellison
Meckel's diverticulum	Vasculitis
Duplication cyst	Potassium
Hemangioma	Infectious causes
	Ulcerative jejunitis

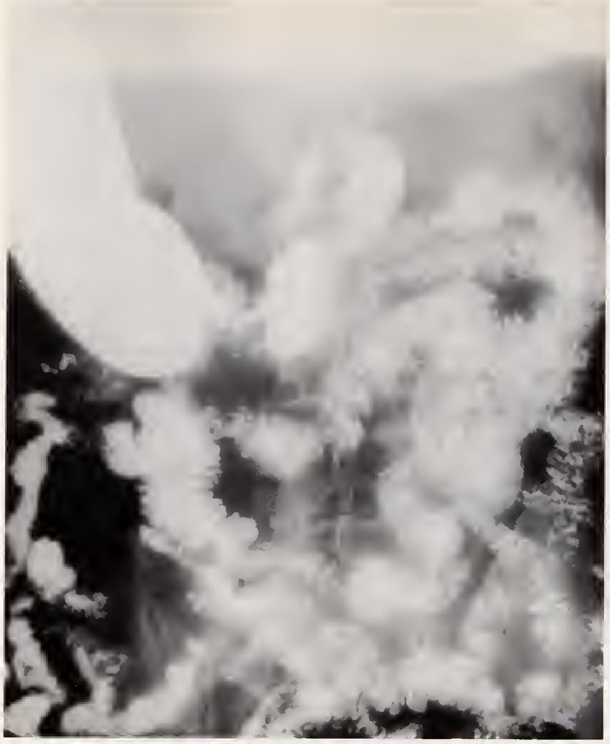


Fig. 2. Small-bowel series revealing cause of bleeding: annular lesion in third portion of duodenum, which routine upper intestinal endoscopy cannot reveal.

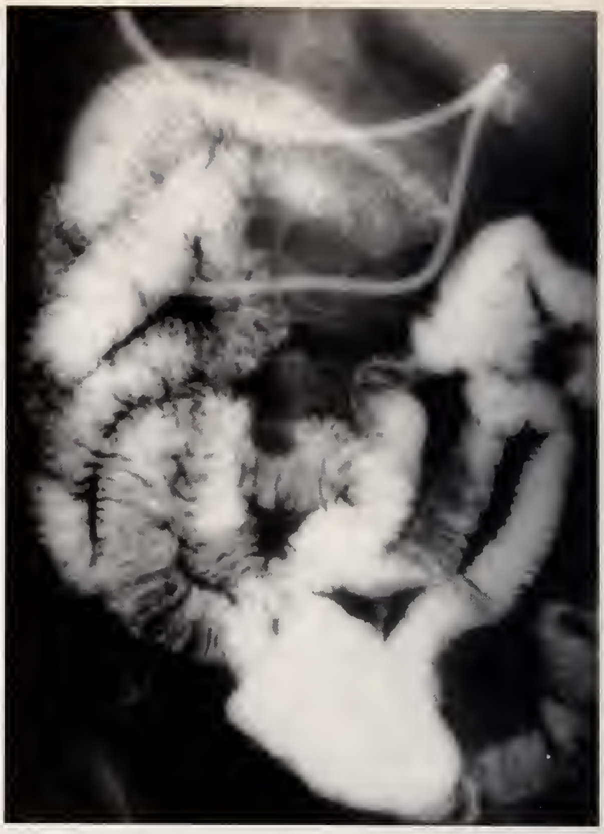


Fig. 4. Enteroclysis of a 46-year-old man who had obscure bleeding; a leiomyoma sits in wall of jejunum.

Fig. 3. Scan shows blood within jejunum. Sometimes nuclear medicine physicians find it hard to tell what piece of bowel this is in. They need to follow the scan over time to see the serpiginous route and the contractions of the small intestine, versus the fixed locations of the colon, to help differentiate those two.

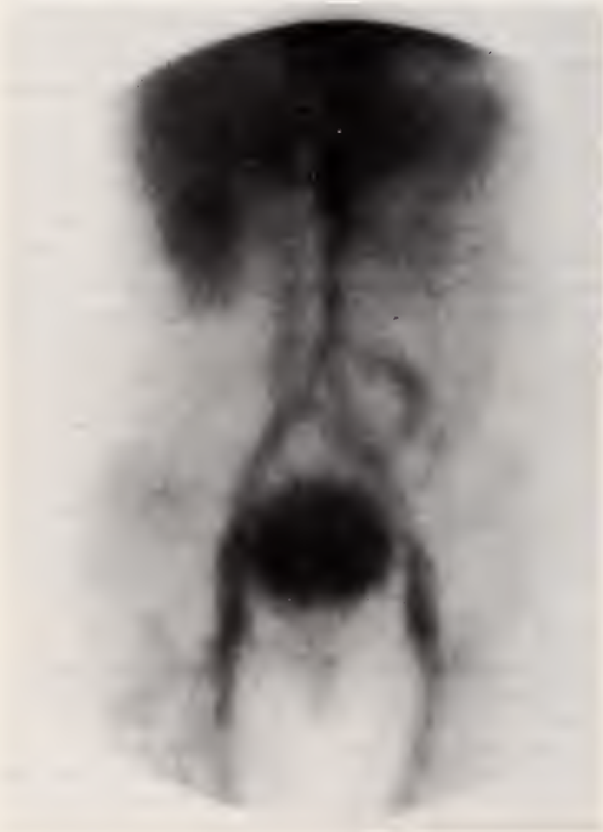
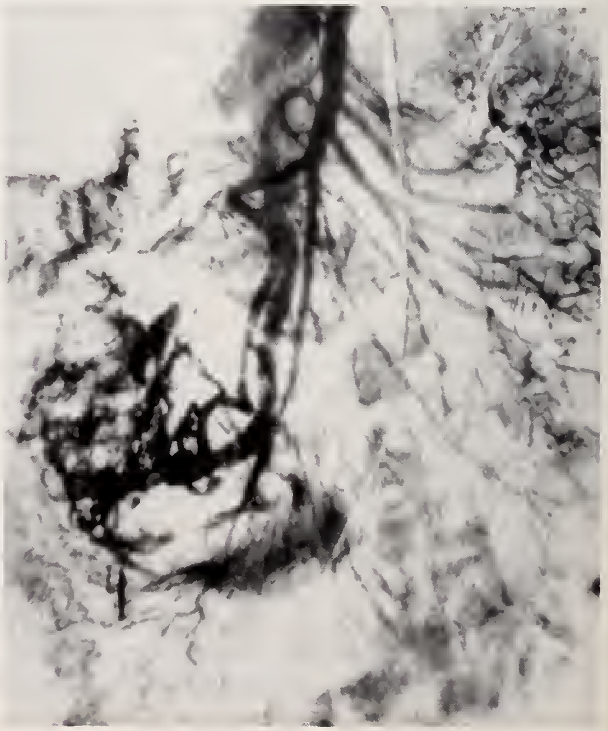


Fig. 5. Cecal angiodysplasia. The two cecal arteries take parallel courses. Some tufting within base of cecum, and an early-filling vein up the middle, characteristic of vascular ectasia. *Courtesy of* John Train.



Scans. How about scans? The days of sulfur colloid scans—those very short scans—are gone. We used to inject sulfur colloid; if it extravasated, a quick blush would appear, and if the person was bleeding, within the three-minute duration of the examination, the physician would be able to pick it out. Nowadays, we withdraw blood from a patient, label it with technetium 99m, and reinject the blood. Patients can then be followed up for as long as 24 hours. As little as 5 cc of intraluminal blood will show up as a blush on the scan screen (Fig. 3).

Still, scans for bleeding do not delineate the exact cause of bleeding within the small intestine: they indicate only the presence and the location of blood. Unfortunately the yields are extremely low with scans.

Enteroclysis. Enteroclysis is not available in many places; in all of Manhattan, I think only one center offers it. Enteroclysis is a double-contrast study of the small intestine. A tube is placed through the patient's mouth or nose and advanced through the stomach to the duodenum. Barium is injected through the tube and fills the small intestine without filling the stomach, avoiding any overlay of stomach and small intestine; methylcellulose can be given as a second contrast agent to give beautiful films (Fig. 4).

It has been reported in the literature that enteroclysis is a gold standard for small-bowel tumors. A positive test indicates a small-bowel tumor; no one doubts that. Unfortunately a negative study does not effectively exclude the presence of a small-bowel tumor; for example, the yield of enteroclysis in a recent large series in patients with obscure bleeding was 10% (5).

Angiography. The medical community puts a great deal of faith in angiography, and it is certainly one of the standard ways to make a diagnosis. Angiography for angiodysplasia is done in several different ways. Certain signs are characteristic: a slowly emptying vein, an early filling vein, and a vascular tuft (Fig. 5). This work again came from Boley's group at Montefiore (6). Extravasation in Boley's series was quite rare.

But are these signs clinically useful? In 1989, the Montefiore group reported that within the small intestine the yield of angiography in obscure bleeding was 14% (7). Angiographic diagnosis of angiodysplasia in the small intestine is difficult, one of the reasons being that there are so many vascular arcades within the small intestine.

Why not heparinize the patient and then perform therapeutic angiography? This has been recommended in the past. Some time ago I received a pamphlet in the mail about the diagnosis of obscure bleeding and its management. I picked up the phone and called the 1-800 number for the promised lecture, which instructed me that if a patient has a negative endoscopy and a negative angiography, I should give the patient anticoagulation agents and then re-angiogram the patient. That course of action has been life-threatening in every patient referred to me after treatment with stress aspirin doses, heparin, or a variety of anticoagulation agents. I have never seen that treatment to be useful; it is risky and I cannot advocate it.

Diagnostic Surgery. If all these simple straightforward tests do not confirm where the bleeding is coming from, why not just operate on the patient, because the disorder is not really a medical but a surgical illness? However, surgery without some type of guidance almost always ends in failure. The literature on the yield of simple exploration dates back to the preendoscopic era, to 1961, when a group out of Boston reported on a hundred patients with obscure bleeding who were taken to the operating room (8). This was before the days of endoscopy, so that they were making the diagnosis at surgery of esophageal varices, or peptic ulceration, or colon cancer, disorders now diagnosed preoperatively. Removing those diagnoses from the results and looking only at the yield for disorders we think routine endoscopies and barium studies would have missed, the yield is 13%. So simple exploration is something that no one should be prepared to do in the obscure bleeder. It has to be coupled with some other form of identification. That is why Jerome Waye of this institution turned to enteroscopy, to try to help these patients; I was fortunate enough as a fellow to be introduced to enteroscopy 6 years ago.

Types of Enteroscopy

The small bowel can be examined endoscopically in several ways:

- Routine upper intestinal endoscopy, esophagogastroduodenoscopy (EGD), can reach the juncture of the second and third portions of the duodenum.
- Push-enteroscopy examination, also called "extended EGD," uses a longer instrument—sometimes a colonoscope—to reach two feet beyond the ligament of Treitz into the jejunum.
- Small-bowel enteroscopy, also called sonde-enteroscopy ("sonde" meaning balloon in French), utilizes a 9-foot-long endoscope with a balloon at its tip that allows peristalsis to carry the

> instrument down through the gut. The small intestine is then examined during the instrument's removal. Nearly the whole small intestine can be examined in this fashion.

All of these procedures can be performed intraoperatively.

Push enteroscopy is straightforward and is routinely performed. It can be used to make diagnoses of patients with obscure bleeding, as well as to obtain small-bowel biopsies in patients with malabsorption, or place jejunal feeding tubes. These instruments can be used both diagnostically and therapeutically; in the duodenum it is possible to see a vascular ectasia and then to place a coagulator through the instrument and cauterize the lesion.

But push enteroscopy still leaves 8–10 feet of small intestine unexamined, and small-bowel enteroscopy, sonde-enteroscopy, has been developed to try to examine that portion of the bowel. Other instruments have been developed, but the state-of-the-art instrument now used in several centers around the country is the 9-ft instrument with its tip balloon. It is a thin instrument, 5 mm in diameter, which is easily and comfortably passed through the patient's nostril. It is not therapeutic, it is purely diagnostic; the bowel wall cannot be marked with it.

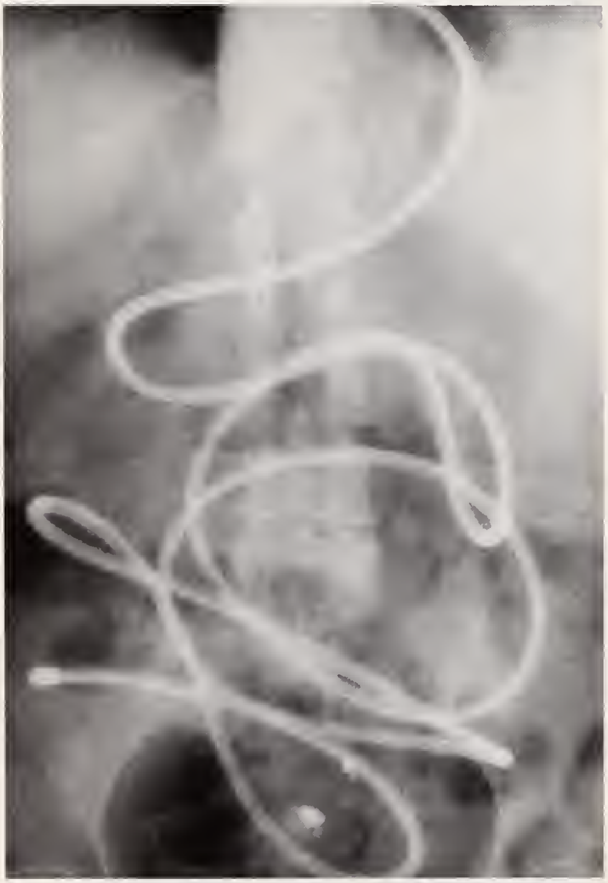


Fig. 6. X-ray showing total small-bowel intubation with enteroscope. Tip of instrument sits at ileocecal valve in right lower quadrant.

The endoscopic portion of the examination is performed during withdrawal, pulling the instrument back, looking through the instrument at that point (**Fig. 6**).

Push enteroscopy and small-bowel enteroscopy are intimately related, because the small-bowel instrument is placed with a push instrument. The small-bowel enteroscope does not permit an adequate examination of the transverse duodenum and the proximal jejunum. Initially a push enteroscope is placed, and the first two feet of the jejunum are examined. If a bleeding site is found there, the rest of the examination is not necessary. The push instrument can then be brought back to the stomach to grasp the little transnasal small-bowel enteroscope, carry it into the jejunum, and leave it there. That really shortens the examination time: previous experience in Japan allowed passive passage through the pyloris, in which patients lay on their right side and waited for the instrument to pass in examinations that extended over 24 hours and more. Jerry Waye's idea of placing it beyond the ligament of Treitz at the start of the procedure means that we can do the entire examination in six to eight hours.

I have now performed more than 480 enteroscopic examinations (9). All patients had obscure bleeding lasting on average over 2 years. Each patient had been transfused an average of almost 18 units of blood and had received over 2 units a month because of ongoing bleeding. All patients had extensive evaluations, more than 1300 upper intestinal endoscopies and 1200 colonoscopies. Many patients had enteroclysis studies and angiography that were nondiagnostic. The average number of examinations for each patient prior to enteroscopy was about 10. We made a diagnosis in approximately 40% of those patients. Vascular ectasias made up the majority of findings, accounting for almost 80%. Small-bowel tumors were the second most common diagnosis (discussed below). We have also found a variety of other lesions, such as Meckel's diverticulum, diverticulosis of the small intestine, and aortoenteric fistula. The yield of push enteroscopy alone is approximately 19%. The additional yield by performing sonde-enteroscopy is 29%. There is some overlap between those two groups; for example, a vascular ectasia is found on the push enteroscopy, then deep in the ileum another lesion is revealed on sonde-enteroscopy. Thus the combined yield is not simply additive; the true yield overall runs about 40%.

Differentiating Small-Bowel Tumors from Vascular Ectasias. Mount Sinai Hospital has some special experience with small-bowel tumors. Asher Kornbluth and I worked together looking at a group of patients who had small-bowel tumors diagnosed at enteroscopy (10). Among the first patients who had small-bowel tumors was one who had an adenocarcinoma of the distal jejunum (**Fig. 7**) that enteroclysis failed to identify.

Asher tried to see if there is a way to differentiate patients with small-bowel tumors from patients with vascular ectasias. You might think that people with small-bowel tumors would have some symptoms: maybe a little weight loss, or a little vomiting, or more copious or more episodic bleeding than patients with vascular ectasias. It was thought that there must be some factor in the clinical history to differentiate those two groups of patients. In fact there is not. When Asher looked at these two groups, they bled similarly, in similar amounts and episodes, of maroon blood or melena, unlike people who truly bled occultly with just fecal occult blood testing. None of these patients had any symptoms whatsoever.

The only real difference was age. It was concluded that patients who were younger have a greater risk of having a tumor as a cause of obscure bleeding than a patient over the age of 60.

After the Diagnosis

What do we do after we make the diagnosis? Surgery seems to be the most straightforward. For a vascular ectasia deep in the small intestine, why not just cut it out? That certainly is a viable approach. But the point is that the person cannot be sent to the operating room simply because somewhere in the jejunum is a vascular ectasia. It has to be localized. The small intestine is different from the colon. In the colon, the surgeon can proceed to take out the right portion or the left portion, as necessary; resection of either portion is a viable plan. But large areas of the small intestine cannot be resected; the person is at risk of becoming a nutritional cripple with terrible diarrhea. The site of bleeding must be marked to limit the resected area.

Certain intraoperative tests have been advocated in the literature to try to help with this problem. Research on two different approaches, intraoperative scintigraphy and intraoperative endoscopy, has been conducted at Mount Sinai.

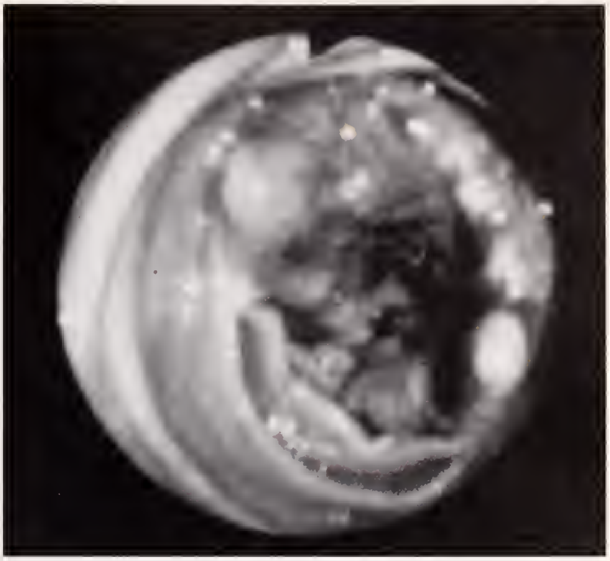


Fig. 7. Adenocarcinoma of large circumference, nearly obstructing the intestinal lumen, that enteroclysis failed to identify. Enteroclysis is not the gold standard many radiologists believe it to be; enteroclysis of this patient revealed no abnormalities.

Intraoperative Scintigraphy. Intraoperative scintigraphy was actually developed at The Mount Sinai Hospital. Christopher Palestro, a specialist in nuclear medicine, has published extensively on it (11). It is a fantastic technique that will, it is to be hoped, catch on in the surgical world. What Pallestro suggested was that if a patient has a bleeding scan indicative of bleeding in the small intestine, they be whisked to the operating room right away, bringing the nuclear medicine scanner along. Then bring out the bowel and scan it to see which portion of bowel contains the radioactive tracer, the radioactive blood. Much run-off takes place when the bowel is manipulated, so the first step in the procedure is to clamp the bowel every 30 cm or so. The blood does not move off somewhere else and give a false reading. Then each bit of clamped bowel is brought under the scanner and examined for the one segment that "lights up." We have recently published a report on a series of patients managed in this way. For this approach to work, the patient must have a positive bleeding scan or a positive angiogram—must, in other words, be actually bleeding.

Intraoperative Endoscopy. Intraoperative endoscopy does not require that the patient be bleeding at the time of surgery. It is possible to put an endoscope into an anesthetized patient and pleat the entire small intestine over the endoscope looking for bleeding sites (**Fig. 8**). At any bleeding site, the surgeon puts a small suture through the serosa marking the spot; then the

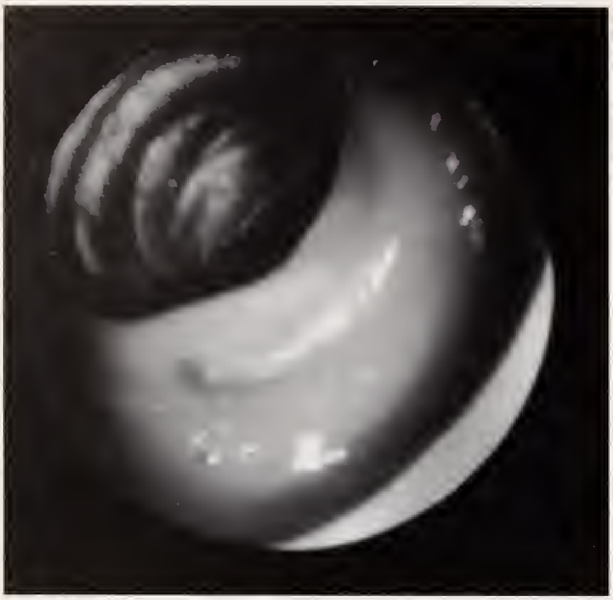


Fig. 8. Angiodysplasia within small bowel using intraoperative endoscopy. An endoscopist knows instantly this is an intraoperative photograph, because room lights are visible through the wall of the bowel—a sign at a regular endoscopy that something has gone wrong.

examination continues throughout the small intestine, each bleeding site being marked with a suture. Finally, the surgeon reviews the sutures: "Three marks here in this part of the bowel, one mark here . . . " and can decide what type of resection, what type of margins, are preferable.

We have recently reported on a series of 23 patients with obscure bleeding who went to surgery using intraoperative endoscopy (12). Given the extensive literature about the yield of intraoperative enteroscopy, we wanted to see if preoperative enteroscopy was a help, a hindrance, or neutral in the management of these patients. The 23 patients were similar to the group discussed above; the average age was 72 years, they had been bleeding for two years, had received an average 28 units of blood, and generally had waited about three months before they decided to go ahead, or their physicians decided to go ahead, with surgery.

Exact correlation between small-bowel enteroscopy and intraoperative endoscopy was obtained in more than three quarters of the patients. But there were discrepancies between those two examinations. The transnasal scope missed lesions in two patients. The instrument does not have a tip to flex, unlike a regular endoscope. There are areas of bowel that are not examined. We estimate between 50% and 70% of the bowel wall is examined with this procedure. Interestingly, intraoperative endoscopy also had a miss rate, and so we considered these two examinations complementary to each other. Using both the preoperative and the intraoperative examination, the yield was better.

Unfortunately, up to 50% of the patients who had surgery in a two-year follow-up bled again. Clearly, surgery is not the final answer for these patients. There has been interest in medical therapy using hormonal agents, which has come to the fore within the last couple of years. I think probably it came to the medical community's attention when Bronner reported on 7 patients who had bleeding from vascular ectasias (13). They were hemodialysis patients, and he treated them with a combination of estrogen and progesterone. Four of the 7 patients stopped bleeding during the follow-up period. So people thought hormonal agents would be perfect for people bleeding from vascular ectasias. There was no control group in his study, but Bronner used his own patients retrospectively as their own control group. They were bleeding before they were put on therapy; they stopped on therapy; and that was considered an excellent result.

Last year, van Cutsem reported a crossover trial using hormonal agents in people with obscure bleeding (14). Half of his patients had Osler-Weber-Rendu or von Willebrand's disease, so it was not an idiopathic group; these were people who had associated illnesses. Still, patients stopped bleeding when the therapy was started and bled again when the therapy was discontinued. We thought, "This is great," because we have patients with diffuse ectasias of the small intestine who are elderly, who cannot undergo surgery or risk a high rate of rebleeding. For them hormonal therapy would be an answer.

So we looked at patients with small-bowel angiodysplasias that we considered inoperable, because they had too many lesions, too diffusely scattered in the small intestine (15). We used drugs similar to Bronner's: Enovid, a combination of synthetic estrogen and progesterones, or the naturally occurring estrogens in Premarin. There were 64 patients that had diffuse angiodysplasias; 30 patients received hormonal therapy and 34 did not. This is a cohort group; this is not randomized; and the control group came from early in our experience, before hormonal therapy really became known. The two groups matched well in sex and age; neither had a preponderance of associated illnesses like end-stage renal disease or von Willebrand's; they had similar histories of two years of bleeding; similar transfusion requirements; and an average follow-up of over a year in both groups.

Interestingly, both groups stopped bleeding.

About half of the treated group and the untreated group stopped bleeding in the follow-up period. This data makes one rethink Bronner's data; he had no control group and his stoppage rate was 57%. We concluded that hormonal therapy was not effective in controlling bleeding from vascular ectasias, especially patients without associated renal failure or von Willebrand's or Osler-Weber-Rendu disease.

Summary

I want to convey the notion that enteroscopy has opened many doors, and continues to open up more doors, in understanding and diagnosing diseases of the small intestine. The true nature of small-bowel angiodysplasia is still unanswered. It seems unlikely that the lesions in the small bowel are similar to the lesions that Scott Boley talks about in the right colon. I doubt that the intermittent obstruction to venous outflow, theorized in the colon, is the pathophysiologic change in the small intestine. Those studies, trying to look for the changes that Boley described, need to be done. We are trying to better characterize angiodysplasia of the small intestine, understanding where they occur, with how many lesions, and whether they are associated with any other illnesses. We are looking at the association of small-bowel vascular lesions with lesions in the stomach and colon. Enteroscopy will in the future, we hope, answer these questions. Enteroscopy, especially push enteroscopy, can help us with the treatment of angiodysplasias.

We are now evaluating new instruments that reach not just two feet beyond the ligament of Treitz, but the entire jejunum, reaching 6 feet beyond the ligament of Treitz (16). Enteroscopy facilitates clinical research, can be used in patient care, and guides treatment.

Questions and Answers

Sachar: We've heard about small-bowel enteroscopy from the one person in the country who has had more experience in this technique than anybody else. Although lots of people have experience with techniques, again it's to Blair's credit and again in the Mount Sinai tradition that this experience hasn't been just a technique performed, a technique that's been used, but has been studied, analyzed, and put to research and scholarly uses while it is being used. Blair, I wanted to ask you a sort of question for today and a question for tomorrow.

Today, where does small-bowel enteroscopy fit into that algorithmic sequence of studies? At what point is it appropriate to do it? At what point should other things be done first?

For tomorrow, when do you predict some therapeutic potential will be built into the scope?

Lewis: Unfortunately, small-bowel enteroscopy is not going to be ordered on admission along with the complete blood count and the SMA 6. Enteroscopy is for the patient who continues to bleed from an unknown source, perhaps after two or three colonoscopies have failed to yield a diagnosis. I think that's appropriate. The yield increases with increased numbers of examinations, to a point. I think that small-bowel vascular ectasias are the minority of the causes of bleeding. Cecal vascular ectasias far outnumber small-bowel vascular ectasias as a cause of bleeding. Examinations may need to be repeated; that's number one. Number two is that the patient's bleeding must be really obscure—the patient must have an ongoing transfusion requirement. I think that enteroscopy is something that you consider when you're thinking about doing an angiogram. I think that our batting average is probably better than angiography. So if you're thinking about doing an angiogram, you should think about enteroscopy. That's today.

For tomorrow, the instrument is really a state-of-the-art instrument. Although it would be nice to have therapeutic modalities through this instrument, when we tried to develop that type of instrumentation, it became too thick and heavy. It will not pass down through the entire small intestine. So I don't think that's in the near future. I think that the greatest hope is the new push enteroscope I discussed; it can treat the entire jejunum. That still has bugs in it, although we've had some early experience here.

Sachar: Blair, you mentioned that in some patients multiple lesions have been found within the small bowel. If you exclude Osler-Weber disease, do you find ectasias in other systems besides the gut very often in these patients, and is that ever a problem?

Lewis: These are not patients who have cerebral ectasias or mucosal lesions or anything else that points us in a direction. These are isolated lesions, and generally, the number of lesions most people have is between two and five, and the lesions tend to be grouped together in one bit of bowel. That just tends to be their course.

Levitt: Can you tell us something about the rationale for hormone therapy?

Lewis: The rationale is an old story going back to Koch's 1952 report on a woman with Osler-Weber-Rendu disease who had terrible epistaxis that varied with her menstrual cycle (17). People then started to use hormonal therapy on epistaxis in Osler-Weber-Rendu disease. In the ear-nose-throat literature, many case reports suggested success with this type of therapy. Finally in 1981 a randomized trial showed that the treatment was ineffective (18). But the ball was then picked up again, and there were several case reports on the use of hormonal agents in people who were bleeding from angiodysplasia of the bowel; then came the works of Bronner and van Cutsem (13, 14).

How does it work? Simply, nobody knows. Hormonal therapy is known to shorten bleeding times in dialysis patients. In the nostrils of patients with Osler-Weber-Rendu disease, studies show hormonal therapy thickens the mucus membranes, putting a distance between the actual blood vessel and the luminal orifice.

Sachar: I wonder if Dr. Levitt wants to know what there is about end-stage renal disease that makes these lesions different?

Levitt: We have a lot of this in our dialysis population. The blood pressure in those patients bounces up and down. Is this a factor?

Lewis: Not that I'm aware of.

Sachar: Why does it happen in the stomach? Is there a particular pathophysiology of the lesions in end-stage renal disease?

Lewis: No one knows the pathophysiology of gastric or small-bowel angiodysplasia. Boley's theory that these lesions in the colon are related to intraluminal pressure has come under fire. Studies looking at actual intraluminal pressures in the cecum do not bear out his ideas.

Sachar: Are the lesions more frequent in renal disease, or are they just more likely to bleed?

Lewis: Well, I think they are more common, because these lesions appear in patients who have renal disease and not in normal individuals. The incidence of cecal angiodysplasia runs between 2% and 3% in the population of normal persons who have not had bleeding, based on endoscopic studies and autopsy series. So the lesions occur naturally in the colon, what Boley calls a common degenerative change of aging, but they do not necessarily bleed.

Sachar: Dr. Lewis left us in his talk with a note of hope that the future of enteroscopy may answer some of these questions. If it does, the answers will come from him and from the Mount Sinai team.

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The Pharmacology of Antiinflammatory Agents:

A New Paradigm

Bruce N. Cronstein, M.D.

Inflammation is the final common response to a variety of noxious stimuli, for example bacterial invasion and trauma. Properly directed, inflammation is the first step in wound healing. Although beneficial with respect to elimination of cellular debris or destruction of invading microorganisms, inflammation may, however, lead to injury of host tissue. Indeed, joint destruction in arthritis and much of the damage to the myocardium incurred during myocardial infarction can be ascribed to an appropriate inflammatory response occurring at an inappropriate (or unfortunate) site. The results of recent studies have led to both an improved understanding of the factors governing inflammation and, more importantly, to new approaches to the control of inflammation in such diseases as rheumatoid arthritis.

Inflammation is characterized by the accumulation of leukocytes which, in the main, mediate the inflammatory process. Recently we have witnessed the biochemical dissection of inflammation: a molecular understanding of those factors which attract leukocytes to sites of inflammation and the biochemical events occurring in leukocytes as they respond to inflammatory stimuli. Moreover, in the past six years we have become aware of the central role of the endothelium in directing leukocytes to specific sites of inflammation.

A large number of chemoattractants and inflammatory mediators have been the subject of study. Among these mediators are the mast cell product histamine, serum factors (complement and the kinin and clotting systems), neurotransmitters (substance P, ATP), lipids (platelet activating factor, lysolecithin, arachidonic acid), eicosanoids (leukotrienes and prostaglandins), growth factors (TGF-β) and, of great interest, the family of proteins known as cytokines. Many of the mediators listed above act as chemoattractants and direct stimuli for neutrophils; others stimulate endothelium to produce chemoattractants. Recent studies have demonstrated that many or all of the mediators listed above may be targets for therapeutic intervention in the treatment of inflammation.

As with other physiologic reactions, homeostasis is maintained at the inflammatory site by an appropriate balance of agonists and antagonists. At sites of inflammation cytokine antagonists, antiinflammatory prostaglandins (PGE_1), breakdown products of cellular constituents with antiinflammatory activity (adenosine), and lipid messengers with antiinflammatory activity (lipoxins) are generated at sites of inflammation in order to dampen the inflammatory response. Current therapeutic approaches to the treatment of inflammatory diseases such as rheumatoid arthritis and inflammatory bowel disease make use of these approaches. Thus, in recent studies we have demonstrated that one potent antiinflammatory agent, methotrexate, is antiinflammatory by virtue of its capacity to promote the release of adenosine (1). Exogenous PGE_1 is currently under study for its use in the treatment of such inflammatory disorders as systemic lupus erythematosus.

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Neutrophils, the primary cells of acute inflammation, are short-lived cells that make their way to sites of inflammation via the bloodstream. These cells roll along the walls of the microvasculature until they encounter an appropriate attractant or adhesive molecule. At that point they adhere to the endothelium, migrate out between endothelial cells into the extravascular space, and migrate toward the inflammatory locus. For many years it was thought that chemoattractants generated in the extravascular space attracted neutrophils to sites of inflammation. In this paradigm of inflammation the endothelium plays a passive role in the direction of the inflammatory process.

At sites of inflammation a variety of chemoattractants are generated. Activation of the complement system leads to generation of the potent chemoattractant C5a. A variety of cells metabolize arachidonic acid to bioactive derivatives, such as LTB_4 and HETEs, which may also act as chemoattractants. Plasma membrane lipids are converted to PAF, which also attracts neutrophils. More recently, cytokines (IL-8) and neurotransmitters (Substance P) have also been shown to be chemoattractants for neutrophils. In general all of the substances listed above interact with specific receptors on the neutrophil. Most of these receptors have now been cloned and their putative structure elucidated; they belong to a family of G-protein-associated receptors (2). Reibman, in collaboration with my laboratory, has recently demonstrated that TGFβ is an extremely potent chemoattractant for neutrophils and that chemotaxis toward this molecule is not mediated by a G-protein-related receptor (3).

The validity of the neutrophil-chemoattractant model of inflammation depended on the capacity of the neutrophil to increase its adhesiveness for endothelium on contact with chemoattractants. This suggested the hypothesis that neutrophils must express or upregulate one or more molecules that mediate adhesion of neutrophils to endothelium. The presence and importance of at least one of these molecules was first demonstrated in the early 1980s as a result of a combination of astute clinical investigation and molecular biology. Several families were described in which children inherited, in an autosomal recessive fashion, a propensity to develop recurrent and severe bacterial infections. The neutrophils and other leukocytes of these patients were found to lack on their surface molecules which, at the time, were known only as myeloid differentiation antigens (CD11a,b,c/CD18, also known as the β2 integrins). Subsequently, these molecules were shown, on the neutrophil surface, to be required for phagocytosis of complement-opsonized particles and, more strikingly, for adhesion to endothelium or other surfaces (4–7). The β2 integrins are heterodimers with a common β-chain (CD18) which is not expressed in the children suffering from leukocyte adhesion deficiency (LAD). Subsequently other surface molecules of the neutrophil have been shown to mediate adhesion to endothelium as well (L-selectin or LAM-1); moreover, L-selectin cooperates with CD11a,b,c/CD18 during interaction of neutrophils with the surface of the endothelium (8–10).

Emigration of leukocytes into inflamed extravascular loci occurs almost exclusively at the postcapillary venule. The chemoattractant-leukocyte model of inflammation does not explain the exquisite localization of the inflammatory response to the postcapillary venule. If the determinant of neutrophil accumulation at sites of inflammation is the encounter between the neutrophil and a chemoattractant, why should one particular site in the microvasculature be the only site at which leukocytes adhere and migrate out into the extravascular space? In 1985 Bevilacqua and co-workers first demonstrated that cultured endothelium exposed to IL-1 were more adherent for resting neutrophils (11). This group subsequently demonstrated that tumor necrosis factor and endotoxin were equivalent with respect to their capacity to induce adhesiveness of endothelium and identified the endothelial adhesive molecule (E-selectin or ELAM-1 [12–14]). Studies performed in vitro demonstrated that, in response to perfusion of an inflammatory agent, E-selectin is expressed only on the endothelium of the postcapillary venule (15). Thus the localization to the postcapillary venule of the capacity to respond to inflammatory stimuli explains why the inflammatory response is channeled into the extravascular space at a specific focus in the microvasculature.

The observation that endothelial cells could express an adhesive molecule in response to inflammatory stimuli opened up an entirely new area of research. Subsequently two other endothelial molecules were shown to be expressed on the surface of endothelium in response to inflammatory stimuli: molecules P-selectin (GMP-140) and ICAM-1 (16–21). P-selectin, E-selectin, and ICAM-1 are expressed or upregulated and then down-regulated in a sequential fashion. P-selectin, a molecule present in the granules of endothelial cells, is expressed within minutes after exposure to stimulus and disappears from the surface by two hours after stimulation. E-selectin is detectable on the surface of endothelium within one hour of stimulation and disappears from the endothelial surface by 12 hours. ICAM-1 is expressed constitutively and its surface expression increases more slowly (18 hr) and is maintained for longer periods (48 hr).

There are two other mechanisms by which endothelial cells direct the inflammatory response. Endothelial cells secrete the chemoattractant IL-8 into the extravascular space thus attracting neutrophils out of the vasculature (22). In addition the endothelium generates the chemoattractant PAF and expresses PAF on its surface (23). Neutrophils adhere to and are stimulated by the PAF on the surface of the endothelium, reinforcing the adhesion to P-selectin and E-selectin. Thus, the endothelium has evolved several mechanisms designed to attract neutrophils to specific inflamed sites.

The Mechanism of Action Of Corticosteroids

Although corticosteroids have been used to treat inflammatory disease for nearly four decades the mechanism of action of these agents is not completely understood. Various hypotheses have been proposed to account for the antiinflammatory effects of steroids; these include "allosteric" effects on proteins (24), stabilization of lysosomal and other cellular membranes (25, 26), redirection of lymphocyte traffic (24, 27–33), direct inhibition of various phospholipases (34), the induction of such proteins as lipocortin (34–38), and inhibition of the transcription of various cytokines and metalloproteases (39–48). However, none of these hypotheses completely account for many of the pharmacologic effects of glucocorticoids: leukocytosis (49), inhibition of leukocyte recruitment to inflamed areas (50, 51), retention of lymphocytes in the lymphatic circulation with shrinkage of peripheral lymph nodes (32, 33), and the promotion of microbial infection (28, 33).

We therefore proposed the hypothesis that corticosteroids are antiinflammatory by virtue of their capacity to inhibit the expression by endothelium of adhesive molecules upon stimulation with endotoxin or cytokines. We found that dexamethasone at low concentrations (0.1–100 nM) inhibits the capacity of endotoxin-stimulated endothelium to become more adhesive for neutrophils. To confirm that dexamethasone was acting at its receptor, we determined whether the steroid antagonist RU-486 could reverse the effects of glucocorticoids on stimulated endothelial adhesiveness (**Fig. 1**). Since RU-486, the potent steroid antagonist, completely reversed the effects of dexamethasone on stimulated endothelial adhesiveness, we concluded that dexamethasone was acting at its receptor to inhibit endothelial adhesiveness. We next determined the effect of dexamethasone on expression of specific adhesogens on the surface of the endothelium and observed that dexamethasone inhibits the stimulated expression of E-selectin (ELAM-1) and upregulation of ICAM-1 on endothelium. Again, RU-486 completely reversed the effects of dexamethasone on E-selectin and ICAM-1 expression. Dexamethasone blocked the IL-1- and endotoxin-stimulated accumulation of mRNA for E-selectin, suggesting that glucocorticoids interfere, at the transcriptional level, with expression of inflammatory adhesogens on the surface of stimulated endothelium. Surprisingly, dexamethasone did not inhibit TNF-stimulated adhesiveness of endothelium for neutrophils or the accumulation of mRNA for E-selectin.

These studies indicate that steroids, in addition to their capacity to block the production of inflammatory messengers such as cytokines, blunt inflammation by inhibiting, at the transcriptional level, the upregulation of adhesogens on the surface of endothelium.

The Mechanism of Action Of Methotrexate

Methotrexate is a folate antagonist first introduced for the treatment of malignancies. Very soon after its introduction, methotrexate was used in the therapy of an inflammatory disease, rheumatoid arthritis (52); however, methotrexate was not widely used for another thirty years, in the early 1980s, when interest in this agent revived. Low dose oral methotrexate has recently been approved by the FDA for use in the treatment of rheumatoid arthritis. Since approval for use in the treatment of RA, methotrexate is now one of the most commonly used second-line antirheumatic agents (53).

Unlike most other antirheumatic agents, methotrexate dramatically diminishes inflammation without diminishing the accumulation of inflammatory cells. Indeed, one recent study demonstrates that there is a greater number of neutrophils in the synovial fluid from patients with rheumatoid arthritis being treated with methotrexate (54). Moreover, unlike corticosteroids, methotrexate does not diminish the chronic inflammatory infiltrate present in the synovium of patients with rheumatoid arthritis. Despite the presence of an inflammatory infiltrate similar in

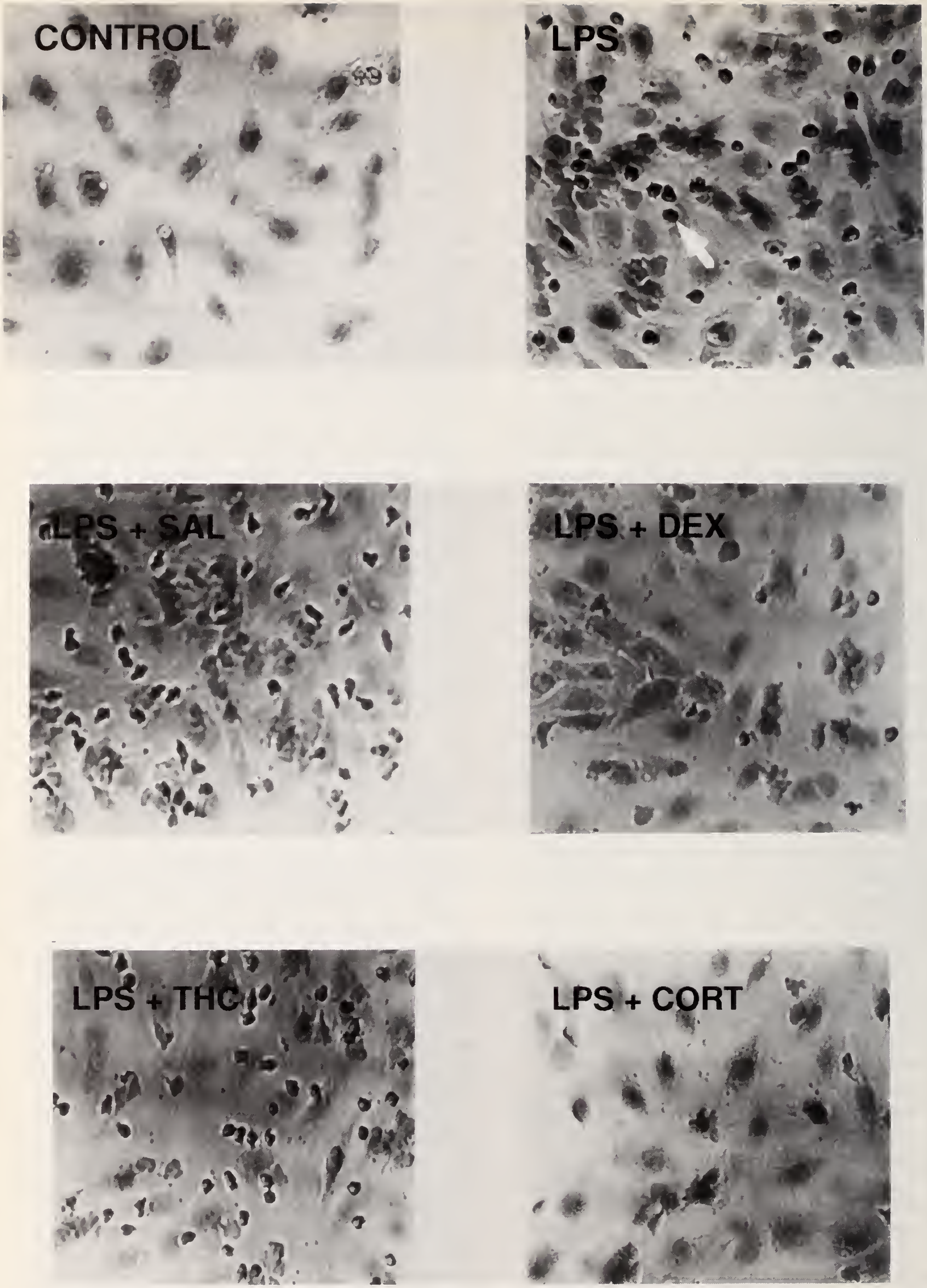

Fig. 1. **Top panel** Treatment of endothelial cells with endotoxin (LPS, 1 μg/mL for 4 hr at 37°C) renders the endothelium more adhesive for neutrophils (white arrow). **Middle panel** Treatment of endothelial cells with endotoxin in the presence of sodium salicylate (SAL, 1 mM) or dexamethasone (DEX, 100 nM). **Bottom panel** Treatment of endothelial cells with endotoxin in the presence of the inactive steroid analog tetrahydrocortisol (THC, 10 μM) or cortisol (CORT, 10 μM).

composition and bulk to that present in the joints of patients who are untreated, methotrexate clearly ameliorates the inflammation of rheumatoid arthritis. Thus, methotrexate must diminish the capacity of the cells of inflammation to induce those changes in the joint which characterize rheumatoid arthritis.

Despite widespread clinical use, the mechanism of action of methotrexate has remained a mystery. A number of clinical observations suggest that methotrexate does not suppress inflammation in rheumatoid arthritis by inhibition of dihydrofolate reductase alone ("folate antagonism") with the consequent inhibition of purine and pyrimidine biosynthesis. Unlike high-dose methotrexate, the low doses of methotrexate used to treat rheumatoid arthritis are rarely toxic to the bone marrow. Indeed, bone marrow toxicity, an expected side effect of high-dose methotrexate, is an indication to stop or lower the dose of methotrexate. Two recent blinded clinical studies demonstrate that neither folate supplements nor citrovorin rescue reverses the therapeutic effects of methotrexate in the therapy of rheumatic arthritis (55, 56).

Recent advances in our understanding of the metabolic fate of methotrexate have suggested an explanation for the effectiveness of intermittent administration of even low doses of methotrexate. Methotrexate is rapidly taken up by cells and metabolized to a series of polyglutamated derivatives which persist intracellularly (57). Polyglutamated methotrexate is an active inhibitor of several enzymatically mediated steps involved in synthesis and metabolism of purines and pyrimidines (58–61). Of note, the enzyme most sensitive to inhibition by polyglutamated methotrexate is AICAR transformylase (Ki = 60nM) (59–61) (**Fig. 2**).

We have found that methotrexate, presumably via inhibition of AICAR transformylase and accumulation of AICARibotide, induces release of adenosine from fibroblasts and umbilical vein endothelial cells. The doses of methotrexate required for promotion of adenosine release are well within the range which can be achieved during antirheumatic therapy of rheumatoid arthritis (EC_{50} 1 nM). Pretreatment of endothelial cells or fibroblasts with methotrexate also inhibits, in parallel, neutrophil adherence (stimulated and unstimulated) to these connective tissue cells (IC_{50} 9 nM). Methotrexate inhibited neutrophil adherence to connective tissue cells by increasing adenosine release, since addition of adenosine deaminase to the supernatant medium completely reversed the effect of methotrexate pretreatment on neutrophil adherence without, itself, affecting adherence (Fig. 2) (1). Thus, we showed that methotrexate promotes release of adenosine from connective tissue cells which inhibits both unstimulated and stimulated adherence of neutrophils to connective tissue cells. Our observations suggest that the antiinflammatory actions of methotrexate in vivo may also be mediated by increased adenosine release at sites of inflammation.

At present the biochemical mechanism by which methotrexate promotes adenosine release remains a matter of speculation. Recent evidence suggests that the accumulation of AICARibotide intracellularly induces adenosine release. When Gruber et al. (62) administered the cell-permeable, nonphosphorylated analog of AICARibotide, AICARiboside, to dogs there was a marked rise in adenosine release from ischemic cardiac tissue that was postulated to be due to inhibition of AMP deaminase. Subsequently, Barankiewicz and colleagues have suggested that AICARiboside (and, therefore, intracellular AICARibotide) inhibits adenosine utilization by cells (63). Our observation that AICARiboside promotes adenosine release and inhibits neutrophil–connective tissue cell interactions is consistent with the hypothesis that methotrexate inhibits the conversion of AICARibotide to FAICARibotide by AICARibotide transformylase and promotes the intracellular accumulation of AICARibotide, which, in turn, promotes adenosine release. We have also examined the effect of AICARiboside on both adenosine release from and neutrophil adherence to either fibroblasts or endothelial cells. We found that AICARiboside, like methotrexate, also promoted adenosine release and inhibited unstimulated and stimulated neutrophil adherence to fibroblasts and endothelium. In a manner identical to that of methotrexate, removal of extracellular adenosine by addition of exogenous adenosine deaminase completely reversed the effect of AICARiboside on neutrophil adherence. Thus, our results are consistent with the hypothesis that methotrexate promotes adenosine release by interfering with intracellular metabolism of AICARibotide (1).

The mechanism by which adenosine modulates inflammatory cell function has been well established; adenosine occupies specific receptors on neutrophils, monocytes, and lymphocytes. In general, as we first showed for the neutrophil, the antiinflammatory and immunomodulatory effects of adenosine are mediated by occupancy of A_2 receptors (64–77). However, in vivo studies suggest, based on the efficacy of receptor-specific analogs,

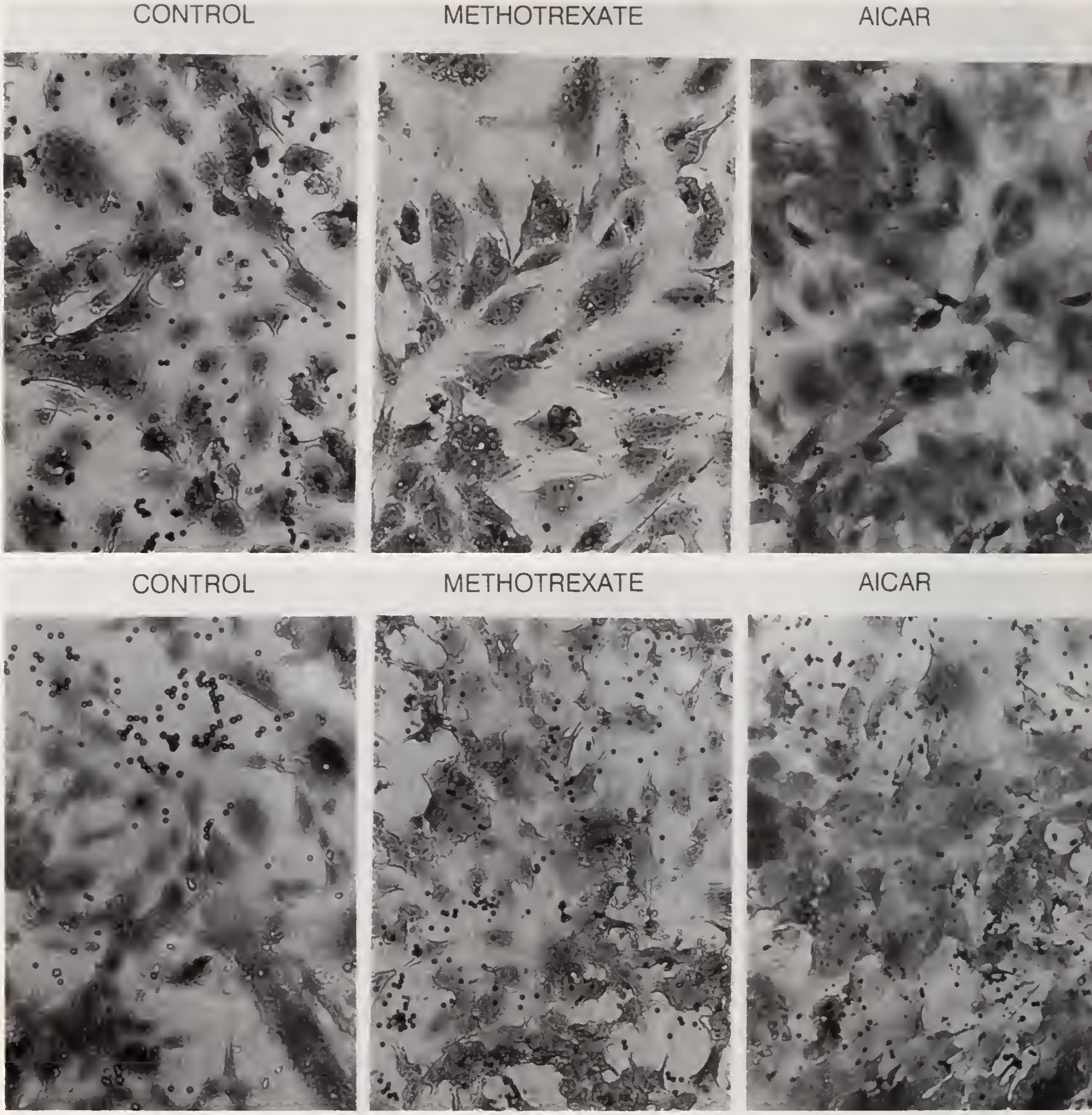

Fig. 2. Top panel Treatment of endothelial cells with methotrexate (100 nM, 48 hr at 37°C) or AICARiboside (100 μM, 2 h prevents adhesion of stimulated (FMLP, 100 nM) neutrophils to endothelium. **Bottom panel** Adenosine deaminase (0.12 IU/mL) reverses the effect of methotrexate pretreatment and AICARiboside treatment on adhesion of stimulated neutrophils endothelium.

that adenosine and its analogs may engage A_1 receptors to suppress acute inflammation (Fig. 3).

Thus, the studies described above demonstrate a novel mechanism of action for the antiinflammatory drug methotrexate. Moreover, this new understanding of the mechanism of action of one of the most commonly used second-line agents for the treatment of rheumatoid arthritis suggests that new, more effective, and safer agents can be developed for the treatment of rheumatoid arthritis that take advantage of the local release of antiinflammatory agents at sites of inflammation.

Conclusion

The studies discussed here demonstrate tha one of the central events of inflammation is th adhesion of neutrophils to endothelium, whic must precede the emigration of these inflammatory cells into the extravascular space. The mechanism of action of two potent antiinflammator agents, corticosteroids and methotrexate, are bes

THE EFFECTS OF ADENOSINE RECEPTOR OCCUPANCY
ON STIMULATED NEUTROPHIL FUNCTION

FUNCTION	A_1	A_2
Chemotaxis	↑	–
Phagocytosis	↑	↓
Superoxide anion, H_2O_2, etc.	–	↓
Adhesion	↑	↓

Fig. 3.

explained as inhibition of neutrophil-endothelial interactions by two different mechanisms. Corticosteroids blunt the capacity of the stimulated endothelium to express adhesive molecules on its surface, whereas methotrexate induces the endothelium to release the potent antiinflammatory autocoid adenosine.

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Asthma:

An Inflammatory Disease

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Asthma has been thought of as a reversible obstructive lung disease in which inflammation played little or no role. Over the past 15 years, however, it has become evident that asthma is a chronic inflammatory disease (1), similar to the rheumatologic disorders, which contributes both directly and indirectly to the obstructive process. The mechanisms leading to this inflammation are multiple and complex. The presence of inflammatory cells and their mediators in the airways produce alterations in bronchial epithelial cells that lead to their destruction and to increased smooth-muscle hyperreactivity characteristic of asthma (2, 3). Evidence for the prominent role of inflammation in asthma comes from morphologic studies demonstrating the presence of inflammatory cells, including neutrophils, mononuclear cells, and especially eosinophils, in the airway associated with mucosal edema (4). Other investigators have demonstrated increased numbers of eosinophils and mast cells in bronchoalveolar fluid (BALF) (5) from asthmatics during mild flareups of disease and increases in these cells in the sputum of asthmatics during mild exacerbations (6). Even in patients who have the mildest asthma, the mucosa has been demonstrated to be abnormal, showing mast-cell degranulation with widespread eosinophilic infiltration coupled with increases in mucosal neutrophils and mononuclear cells (7, 8).

If asthma is an inflammatory disease and if proinflammatory cellular infiltration is a disease characteristic, how is the presence of these cells responsible for the onset of disease? Proinflammatory cells like eosinophils and mast cells, when activated, release both stored and newly synthesized mediators, including cytokines, which have a wide variety of biological activities (9). These mediators are responsible for the clinical features of asthma, including bronchoconstriction, microvascular leakage, edema, exudation, and mucus hypersecretion (10–12).

Atopy and Asthma

Although asthma was once considered a disease occasionally associated with allergic factors, several recent large studies have clearly established a connection between atopy and asthma in a large percentage of asthmatics. These studies have come primarily from rural and suburban populations and have associated either elevated IgE levels or positive radioallergosorbent tests (RASTs) to a limited number of aeroallergens with emergency visits for asthma treatment (13–15). Burrows et al. (16) in a large Arizona study found higher IgE levels in 90% of patients below the age of 40 reporting to local emergency rooms for asthma treatment than in age-matched non-asthmatic controls. Similarly, Pollart et al. (17) and Reid et al. (18) in two studies, one in rural Virginia and one in northern California, associated increased emergency visits for asthma in adult patients below the age of 50 with positive RASTs for dust mites and rye grass respectively.

Although the role of atopy and asthma has been investigated in rural and suburban populations, there are relatively few data regarding the role of atopy in inner-city urban asthmatic populations. At The Mount Sinai Hospital in New York City, N.Y., we have investigated the role of

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atopy and asthma in asthmatics coming to the emergency room (19). The mean IgE level of asthmatic patients (n = 73) reporting to the Mount Sinai Emergency Room was 263.8 IU/mL, compared to 63.8 IU/mL in the nonasthmatic control group ($p < 0.032$) (n = 30). Sixty-eight percent of the asthmatics had an IgE level in the atopic range (>100 IU), which is consistent with other data nationwide.

In contrast to the studies of rural and suburban populations, however, the urban asthmatic group we investigated had IgE antibodies directed against an indoor panel of allergens as determined by RAST. Our population was allergic to a predominantly indoor panel of allergens, which provide constant exposure to allergens leading to chronic airway inflammation, including cockroach, cat, dog, and dust mite. This contrasts with studies (13–18) which had demonstrated either IgE antibodies or positive allergy skin tests to grass pollen, ragweed pollen, tree pollen, and mold pollen.

Mast Cells and Asthma

Mast cell populations are not homogeneous, and two major types of mast cells have been described, the mucosal T-type mast cell (MC_T) and the CT-type connective tissue (MC_{CT}) mast cell (20). These cells differ from each other in a variety of ways, including enzyme content and location (**Table 1**). MC_T cells contain tryptase (hence the name T-type); MC_{CT} contain both tryptase and chymase (hence the name CT) (21). MC_T are present in the alveolar wall, bronchi, bronchioles, and nasal and bowel mucosa, whereas MC_{CT} are present in skin, intestinal submucosa, and nasal mucosa (22). Although one type of mast cell may predominate at a particular anatomic site, the other type of mast cell may also be present (22). MC_T and MC_{CT} also differ in the lattice structure of their cytoplasmically stored preformed mediators; the MC_T type mast-cell mediators have a scroll-like appearance, whereas MC_{CT} preformed mediators have a lattice structure with a grading crystal formation (23). MC_T cells are T-cell dependent and their numbers are dramatically higher in parasitic infections and in asthma than in the MC_{CT} (24). In contrast, in T-cell-deficient states, either acquired immunodeficient states or primary T-cell disorders, MC_T are absent (25). Another differentiating point is histamine content. Connective mast cells contain more histamine than the mucosal mast cells (26) and release histamine more readily, in response not only to IgE crosslinking but also to other stimuli, including compound 48/80, codeine, and radiocontrast dye (27).

TABLE 1
Comparison of T-Type (MC_T) and CT-Type Connective Tissue (MC_{CT}) Mast Cell

Characteristic	MC_T	MC_{CT}
Tissue distribution		
Skin	–	+ +
Intestinal submucosa	+	+ +
Intestinal mucosa	+ +	+
Alveolar wall	+ +	–
Bronchi/bronchioles	+ +	+
Nasal mucosa	+ +	+ +
Conjunctiva	+	+ +
Enzyme content	Tryptase	Tryptase Chymase
T-cell dependency	Yes	No
Granule morphology	Grating, lattice	Scroll

Looking at the development of the two mast cell types, it is uncertain whether they are derived from a single uncommitted stem cell which can then become either a MC_T or MC_{CT} or whether they are derived as separate lineages. Mast cells, like basophils, are derived from bone-marrow stem cells (28), but in contrast to other bone-marrow-derived cells, they undergo only partial differentiation in the marrow and complete the differentiation process in peripheral-mucosal and connective-tissue microenvironments (29). MC_T and MC_{CT} arise from hematopoietic progenitor stem cells (28). The progenitor cells with commitment to a mast-cell lineage are released into the circulation. At the time of commitment and soon thereafter, they enter their tissue site of residence and develop along MC_{CT} or MC_T pathways to the final mature forms. Whether the predominance of a particular type of mast cell in different tissue is due to selective recruitment of precommitted mast cells to a particular site is unclear (29). T-lymphocyte-associated activity is important for MC_T cells, whereas fibroblast-derived factors appear to be important in both mast cell types (30).

Allergen-induced mast cell activation through crosslinking of IgE antibodies bound to a high-affinity Fc receptor (FcEI) is associated with both an early phase reaction characterized by the release of preformed mediators, histamine, and the proteolytic enzymes tryptase and chymase, and a late phase reaction (LPR) characterized by generation of proinflammatory mediators (31). The late phase reaction is associated with the recruitment of eosinophils and neutrophils into the airways and is more important than the early

TABLE 2
Pharmacologic Effects of Major Cyclooxygenase and Lipooxygenase Products in Asthma

Mediator	Pharmacologic action
Cyclooxygenase	
PGD_2	Bronchoconstrictor Peripheral vasodilator Neutrophil chemotaxis Tussive agent
$PGF_{2\alpha}$	Bronchoconstrictor Peripheral vasodilator Coronary vasoconstrictor
Lipooxygenase	
LTB_4	Neutrophil and eosinophil Chemotaxis and adherence Vasopermeability
LTC_4	Bronchoconstrictor Vasopermeability
LTD_4	Bronchoconstrictor Vasopermeability
LTE_4	Vasopermeability

phase reaction in propagating airways inflammation (32).

The presence of such a wide variety of mediators has therapeutic implications. For example, although histamine levels are elevated in serum and bronchoalveolar lavage fluid (BALF) of asthmatics, antihistamine therapy in general has been unsuccessful in the treatment of asthma (33). The failure of antihistamines as antiasthmatic agents is not surprising given the large number of mediators involved in this process. The presence of so many mediators makes it unlikely that inhibition of any single one will be sufficient to treat all of the symptoms of asthma.

Mast cell death does not occur from IgE crosslinking activation, and in 24 hours preformed mediators are resynthesized and are present in intracytoplasmic stores ready to be rereleased after subsequent restimulation (34). Immediate mast cell degranulation can be demonstrated clinically by allergy skin testing, in which exposure of allergen to MC_{CT} cells sensitized with allergen-specific IgE results in histamine release. Late phase reactions can also occur with allergy skin testing but generally occur only about 25% of the time for a given dose of allergen. With larger doses of allergen administrated in the early response, LPRs will occur 100% of the time (35). Biopsies obtained from the early response and the late reaction are dramatically different; the early response yield is relatively acellular (36), whereas the late response yield is associated with the accumulation of large numbers of eosinophils and neutrophils (37). The same inflammatory events with cellular accumulation of eosinophils and neutrophils that occur in the skin after skin testing also occur in the airway after allergen exposure.

Synthesized Lipid Mediators

The cyclooxygenase products play an important role in the pathogenesis of asthma. These mediators are capable of causing bronchoconstriction and bronchohyperresponsiveness (Table 2), increased mucus secretion, and microvascular leak, which can cause bronchial obstruction (38). They can cause cough interacting directly with tussive receptors in the airways. The major cyclooxygenase products implicated in asthma are PGD_2 and PGF_{2a} (39), which are 30 times more potent than histamine as bronchoconstrictors (40). Elevated levels of these mediators have been demonstrated in serum of both chronic asthmatics and in BALF from asthmatics after allergen challenge (41). Treatment with cyclooxygenase inhibitors, including aspirin, have only limited efficacy in treating chronic asthma and may even cause exacerbation by as yet undetermined mechanisms (42). The exact role of cyclooxygenase products in asthma is still somewhat uncertain because of the lack of effective inhibitors at more specific sites in the biosynthetic pathway. The development of more specific inhibitors will help elucidate the role of these products in the pathogenesis of asthma.

Leukotriene products can similarly cause airway smooth-muscle contraction, airway hyperresponsiveness, mucus release, and microvascular leak (Table 2) and are among the most potent chemotoxins known for neutrophils and eosinophils (43). LTC_4, LTD_4, LTE_4, and LTB_4 are the principal leukotrienes associated with asthma (44). As bronchoconstrictors, the leukotrienes are one thousand times more potent than histamine and can potentiate the bronchoconstrictive effects of histamine (45). The precise role of leukotriene products in asthma, like the role of cyclooxygenase products, is unclear because of the lack of specific inhibitors. However, clinical trials with more promising agents have given encouraging preliminary results (46, 47) which may lead to more widespread use of these agents.

Platelet activating factor (PAF) was so named because it was first derived from IgE-sensitized rabbit lung tissue and was demonstrated to cause aggregation of platelets (48). PAF is generated by phospholipase A_2, the same enzyme that synthesizes the cyclooxygenase and lipooxygenase products. Instead of producing precursors for arachidonic acid and leukotriene products, lyso-PAF is synthesized, and can then be further metabolized into PAF (49). PAF production is not limited to mast cells; macrophages can also produce significant amounts of this mediator (50). PAF in the airways is a potent bronchoconstrictor, both in normal persons and asthmatics, and if injected in the skin can cause a wheel-and-flare reaction (51). In experimental animal model systems, PAF also causes microvascular leakage, mucus secretion, and edema, which may contribute to airway obstruction (52).

PAF interacts with specific receptors on a variety of cells, including neutrophils and eosinophils (53), and—like the leukotrienes—can cause activation and chemotaxis of eosinophils in vivo and in vitro (54). Activated eosinophils produce several proteins, including major basic protein (MBP), eosinophilic cationic protein (ECP), and eosinophil-derived neurotoxin (EDN), which directly damage the respiratory epithelium (55). PAF, produced either by a macrophage or a mast cell, activates eosinophils to release MBP, ECP, and EDN. The interaction of these proteins with the epithelial cells causes disruption and desquamation and exposes subbronchial unmyelinated fibers (56). Stimulation of the exposed axons by reflex action causes increased bronchial hyperresponsiveness (57). The loss of epithelial cells also results in the loss of an epithelial-cell-derived smooth-muscle relaxing factor which can further contribute to bronchial hyperreactivity (58).

Mast cell activation and elaboration of mediators could explain many of the features of asthma. Activation of mast cells through crosslinking of IgE results in the release of the preformed and newly synthesized mediators, which cause vasodilatation and exudation, accompanied by the infiltration of eosinophils and neutrophils into the site of allergen exposure. At the site of inflammation the neutrophils and eosinophils are activated and release MBP, EDN, and ECP, which interact with the epithelial cells, causing desquamation and exposing the sensory nerve fibers, increasing the muscular tone and the reactivity of the bronchial smooth muscle (Fig.).

Although this model system is appealing, it does not account for a substantial part of the chronic inflammation present in asthma.

T Cells and Asthma

It has become apparent over the past two years that T cells, and the cytokines produced by them, are important cells in propagating the chronic inflammatory process in asthma (59, 60). Evidence for the role of T cells in asthma comes from several studies in which activated peripheral blood T cells expressing increased class II antigens and interleukin 2 (IL-2) receptors are present in asthmatics admitted into the hospital for acute flairups (61, 62). In airway allergen challenge studies of asthmatics, CD4+ T cells can be demonstrated in BALF at 24 hours after the challenge associating T cells and LPRs (63). In allergy skin test studies during the LPR, infiltrating T cells can be demonstrated expressing either the IL-2 receptor or class II molecules (64).

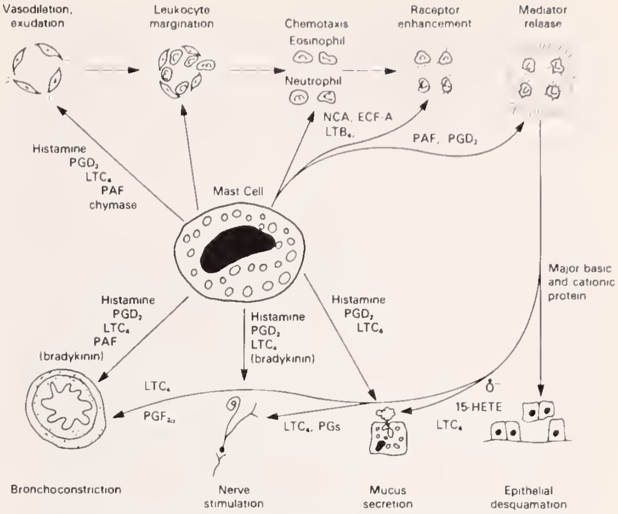

Fig. Schematic view of role of mast and mast cell mediators in pathogenesis of allergic airway inflammation.

A series of important observations made by Mossman and Coffman in murine T-helper-cell model systems have direct implications for allergic asthma (65). T helper (Th) cells can be divided by their cytokine profile into a Th_1 type that produces predominantly IL-2, gamma interferon, and lymphotoxin, and a Th_2 type that produces predominantly IL-4, IL-5, IL-6, and IL-10 (66, 67). Th_1 T helper cells produce cellular responses while Th_2 T helper cells produce humoral responses.

It appears, then, that the type of immune response that develops to a particular allergen depends on the cytokine profile of the T helper cells. An allergic asthmatic will generate Th_2 helper T cells to a series of aeroallergens, whereas a nonatopic individual will develop a Th_1 response. Investigators have isolated T-cell clones specific for allergen (dust mite) from allergic asthmatics that produce IL-4; similar clones from nonatopic nonasthmatic individuals generate gamma interferon in response to the same allergen (68, 69). These observations validate the existence of Th_1 and Th_2 clones in human allergic diseases and could have important therapeutic implications.

Another advance in the understanding of T cells in allergic asthma was the finding that IL-4 is critical for the synthesis of IgE (70). The importance of IL-4 in IgE production was demonstrated in co-culture studies in which stimulated IL-4–producing T cell blasts incubated with donor B cells from nonallergic individuals supported IgE synthesis in vitro (71). In these studies, the ability to maintain IgE synthesis was directly related to the amount of IL-4 produced by the T cell blasts. Furthermore, IgE synthesis could be blocked in culture by adding anti–IL-4 antibody. In another model system, anti–IL-4 antibody blunted polyclonal IgE production in response to parasitic infections, again indicating the important role of IL-4 in IgE synthesis (72, 73). The major biological activities of IL-4 as they relate to allergic asthma are not confined to the ability to induce immunoglobulin isotype switch to IgE but also include activation of other proinflammatory cells like neutrophils and monocytes (74).

Gamma interferon has a biologic effect opposite to that of IL-4; it inhibits IgE synthesis by B cells (75). In complementary studies, T cell blasts were stimulated and co-cultured with donor B cells, and gamma interferon levels were measured in the culture supernatants (76). IgE levels were measured and the opposite effect of IL-4 was observed. The ability to produce IgE by the donor B cells was inversely proportional to the gamma interferon produced by the T cells blasts. Increased gamma interferon production by downregulating IgE synthesis may have an important role in regulating the generation of IgE antibodies. The major activity of gamma interferon as it relates to allergic asthma and the generation of IgE antibodies is to inhibit IL-4 mediated events, especially the IgE isotype switch (77). Gamma interferon has been used to treat patients with the hyper IgE syndrome, a disorder characterized by recurrent skin infections and markedly elevated levels of IgE (78). Gamma interferon therapy dramatically reduced the IgE levels in these patients without affecting IgG, IgA, or IgM levels. This observation has led to several ongoing clinical trials with gamma interferon to treat asthma.

Competition between Th_1 and Th_2 clones may lead to the development of allergic asthma (79). The atopic individual develops Th_2 cells in response to aeroallergens which produce IL-4 and little gamma interferon. Th_2 cells also produce another cytokine, IL-10, that can inhibit gamma interferon production from Th_1 cells (80). Interaction between the two different types of T helper clones will lead to either specific IgE antibodies produced against aeroallergens or a cellular response with no IgE antibodies. Potential novel strategies to treat asthma could include inhibitors of IL-4 (IL-4 receptor antagonists) or inhibitors of IL-10 which block gamma interferon production and similarly would inhibit IgE synthesis. The ability to manipulate this system will undoubedly lead to better and more specific asthma therapy.

Other Th_2 cytokines important in allergic asthma include interleukin 3 (IL-3) and interleukin 5 (IL-5). IL-5 stimulates production and activation of eosinophils (81), which can damage bronchial epithelial cells. IL-5 mRNA has been demonstrated in T cells from bronchoalveolar fluid in the late phase reaction after allergen challenge (82). The local production of IL-5 serves to activate and recruit eosinophils into the airways, similar to the action of platelet activating factor and the leukotriene and cyclooxygenase products. The proliferation and growth of MC_T cells, which are T-cell dependent, is believed to be mediated through the increased local production of IL-3 (83, 84) in response to allergen.

Macrophage and Mast Cell Production of Cytokines

Other cytokine-producing cells have also been implicated in allergic asthma. Alveolar macrophages produce a wide variety of proinflammatory mediators in asthma (85–87). Recent studies have also demonstrated that alveolar macrophages can become activated via crosslinking of a low affinity surface IgE receptor (FcE RII) distinct from the IgE receptor present on mast cells (FcERI) which results in the production of IL-I-B and TNF-alpha (88). This may be important clinically since increased levels of IL-1 have been observed in the bronchoalveolar lavage fluid of nocturnal asthmatics (89). We have similar data for activated monocytes-macrophage products in allergic asthma. Our laboratory has recently described a novel monocyte-macrophage–derived mucus secretagog (MMS-68) that causes mucus-like glycoconjugate release from cultured respiratory epithelial cells (90). We have demonstrated increased spontaneous production of MMS-68 from monocyte culture supernatants in steroid-dependent asthmatics, again suggesting a role for mediators produced by alveolar macrophages in allergic inflammation (91).

Proinflammatory cytokine production is not restricted to T cells and monocytes. Mast cells, in addition to releasing histamine, synthesizing a variety of leukotriene and prostaglandin products, and producing chemotaxic factors for neutrophils and eosinophils, also synthesize cytokines after the engagement of the FcERI (92). mRNA for IL-4, IL-5, and IL-6 can be demonstrated in mast cells after IgE crosslinking (93). The cytokine profile of these mast cells is identical to the Th_2 cell.

Inflammation and Bronchial Hyperreactivity

If such a large variety of proinflammatory cells—mast cells, T cells, macrophages, the eosinophils and neutrophils—cause inflammation in the airway in allergic asthma through the production of mediators, what are the mechanisms involved that lead to bronchoconstriction? Many studies have demonstrated that patients never relate allergen exposure to a clinical flareup of disease. Viral infections or other nonspecific stimuli like exercise and cold air exposure are the major triggers for asthma (94, 95), not allergen exposure. In order to reconcile this apparent contradiction, Cockcroft et al. (96) demonstrated that after allergen challenge, an allergic asthmatic has an increase in nonspecific bronchial hyperreactivity determined by histamine challenge. This means that after allergen exposure, an allergic asthmatic required a lower dose of histamine (PD_{20}) to produce a 20% fall in the forced expiratory volume (FEV1) than after preallergen exposure. This is the first demonstration that allergic airway inflammation can lead to increased nonspecific bronchial hyperreactivity. Seasonal or perennial allergen exposure in the asthmatic patient leads to chronic inflammation in the airway, causing increased bronchohyperreactivity (97). The increased hyperreactivity makes the patient more susceptible to nonspecific asthma triggers like viral infections and exercise (98). The presence of these cells causes increases in airway hyperresponsiveness that can lead to variable airway obstruction and to the symptoms of asthma (99).

Conclusion

If asthma is a chronic inflammatory disease, antiasthma therapy should consist of antiinflammatory medications such as inhaled steroids, not such agents as theophyline and beta agonists, which have no antiinflammatory properties. Many studies have shown that prolonged therapy with inhaled steroids reduces bronchial hyperreactivity (100, 101). Furthermore, Adelroth et al. have shown on bronchial biopsy that treating allergic asthmatics with inhaled steroids leads to reduction in the numbers of eosinophils, neutrophils, and T cells in the airways (102). Further elucidation of both the cellular and molecular events involved in the inflammatory processes in asthma will no doubt lead to more specific and less toxic therapy.

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Prevalence of Atopy in an Inner-City Asthmatic Population

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Abstract

Seventy-three patients at The Mount Sinai Hospital Emergency Room were investigated to determine the prevalence of atopy in asthma in a predominantly black and Hispanic inner-city population. Serum IgE levels and radioallergosorbent tests (RASTs) to eight common inhalant allergens were measured in both the asthmatic group and a nonasthmatic emergency-room control group. The mean total IgE level for the asthma group was 263.8 IU/mL compared to 63.8 IU/mL in the control group ($p = 0.032$), and 60% of the asthmatics had IgE levels in the atopic range (>100 IU/mL). Increases in IgE were associated with age under 50 years but did not reach statistical significance. Cockroach, dust mite, cat, and dog were the most common RASTs in the asthmatic group; there were no positive RASTs in the control group. There was a correlation ($p = 0.04$) between age (less than 50 years) and increased numbers of positive RASTs. These results are similar to those of other studies that have associated atopy with asthma in rural and suburban populations. These data demonstrate that atopy is common in the asthmatic patients seen in The Mount Sinai Hospital Emergency Room and strongly suggest that management of atopic factors should become routine in the care of adult asthmatic patients.

ASTHMA is a chronic inflammatory disease with a multifactorial etiology which affects approximately 5% of the population of the United States (1). Recent national studies have revealed that the incidence and severity of this disease are increasing, especially in inner-city minority populations (2, 3). Although asthma was once considered a disease occasionally associated with allergic factors, several recent large studies have clearly established a connection between atopy and asthma in a large percentage of asthmatics (4–6). These studies of adult patients have come primarily from rural and suburban populations and have associated either elevated IgE levels or radioallergosorbent tests (RASTs) positive for a limited number of aeroallergens with emergency visits for asthma treatment. Burrows et al. (4), in a large Arizona study, found higher levels in 90% of patients below the age of 40 years reporting to local emergency rooms for asthma treatment than in age-matched, nonasthmatic controls. Similarly, Pollart et al. in two studies, one in rural Virginia (5) and one in northern California (6), associated increased emergency visits for asthma in adult patients younger than 50 years of age with RASTs positive for dust mite and rye grass, respectively.

Although the connection between atopy and asthma has been established in these rural and suburban populations, few studies have attempted to identify atopic factors in inner-city minority populations (7). To determine the prevalence of atopy in asthmatics from a predominantly black and Hispanic inner-city population, we measured IgE and RAST levels in 73 asthmatic patients and in 30 age-matched, nonasthmatic control patients seen in The Mount Sinai Emergency Room. The objectives of this study

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TABLE 1

Distribution of Age, Sex, and Race of the Study Population

	Control group (n = 30)	Asthma group (n = 73)
Age	44.7 ± 20.7	45.9 ± 15.3
Sex		
(% female)	64%	65%
(% male)	36%	35%
Race		
(Hispanic)	82%	79%
(black)	15%	16%
(white)	3%	5%

Both the control and asthma group were predominantly Hispanic and black. The mean duration of disease was 14.6 years.

were (a) to assess the prevalence of elevated IgE levels in a population of asthmatics compared to a nonasthmatic control group and (b) to determine which allergens are most common in the asthmatic group.

Methods

Study Population. Patients seen in The Mount Sinai Hospital asthma room from February 1990 to June 1990 were enrolled in this study after they had been evaluated by an emergency room physician and judged to be having acute airway obstruction requiring bronchodilator therapy. Patients were enrolled by two of the investigators (HN and LMY). Peak flow measurements before and after bronchodilator therapy were made with mini-Wright peak flow meter (Armstrong Industries, Northbrook, IL) in 46 of the 73 patients with asthma, and each patient demonstrated marked improvement after treatment. The rest of the asthmatic patients were too ill or unwilling to comply before bronchodilator therapy. Serum samples were obtained from all the asthmatic patients prior to therapy. Demographic data, patient medications, and duration of disease were determined from the emergency room sheets. Serum samples from age-matched controls were also obtained during the same period from patients entering the emergency room for evaluation of medical diagnoses other than asthma, including angina, pneumonia, trauma, renal colic, and upper respiratory infection.

TABLE 2

Distribution of Asthma Medications

	No. of patients
Oral steroids + beta agonist + theophyline	22
Beta agonist + theophylline	3
Beta agonist + theophylline + inhaled steroid	13
Beta agonist + theophylline + inhaled steroid + cromolyn	7
Beta agonist + inhaled steroid	7
Beta agonist	11
None	10

Fifty-two patients, including 22 taking oral prednisone, required multiple medications to control their disease.

Laboratory Assessment. Laboratory measurements for total serum IgE levels were determined by enzyme immunoassay (PRIST) (Pharmacia, Piscataway, NJ). RASTs for timothy grass pollen, elm pollen, ragweed, cat, dog, *Aspergillus fumigatus,* house dust mite, and cockroach were performed utilizing a commercially available kit from Pharmacia.

Statistical Analysis. Statistical analysis was performed using the SAS statistical program package (SAS Institute Inc., Cary, NC). Data were compared using a two-tailed Student t-test. An alpha value of 0.05 was established as the criterion for statistical significance.

Results

Study Population. The asthmatic population of 73 was composed of 64% women and 36% men; the control group of 30 was composed of 70% women and 30% men. The mean age of the study population was 45.9 years (range 18–74 years), and the mean age of the control group was 44.7 years (range 18–67 years). Sixty of the asthmatic patients were Hispanic, 11 were black, and 2 were white. There were 40 Hispanic women, 7 black women, 20 Hispanic men, 4 black men, and 2 white men. Eighteen patients were older than 50 years, and 55 were younger than 50. The population used in this study reflects the demographics of the community that surrounds The Mount Sinai Hospital (see **Table 1**).

The severity of asthma in the study group is reflected in the mean duration of disease, 14.6 years (range 2 months to 30 years), and the amount of medications required to control the asthma. Fifty-four of the 73 asthmatics, including 22 who were taking oral prednisone, required multiple medications to control their disease (Table 2).

Incidence of Elevated IgE Levels in Asthmatic Patients. Figure 1 illustrates the range of distribution of IgE values in both the asthmatic and control groups. There is a statistically significant difference (p = 0.032) between the mean IgE level for the asthmatic group, 263.84 IU/mL

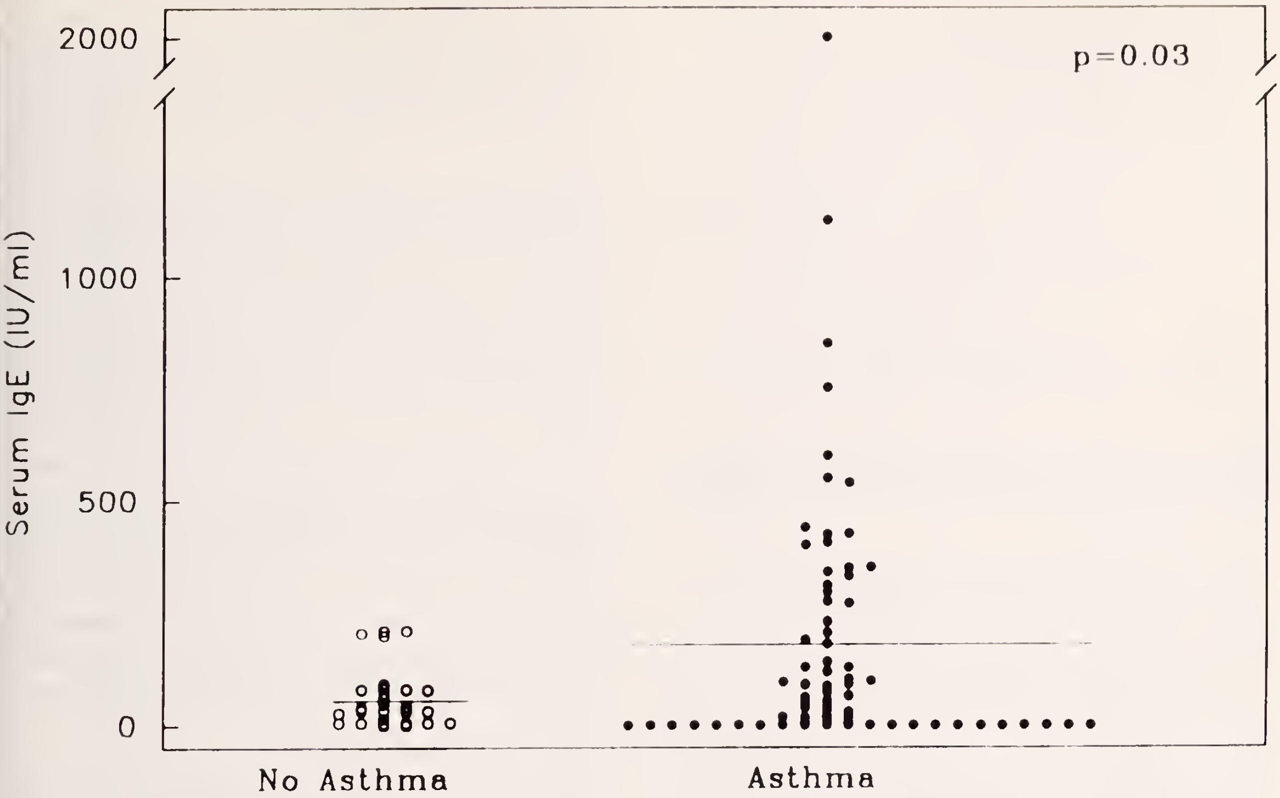

Fig. 1. Distribution of IgE levels in asthmatic and control groups. IgE levels are significantly ($p = 0.03$) increased in the asthmatics.

(range 0–2000 IU/mL) and the control group, 63.3 IU/mL. There were no statistical differences in IgE levels either between men and women or between blacks and Hispanics in the asthmatic or control groups. Fifty of the 73 asthmatic patients had IgE levels greater than 100 IU/mL, which is defined as the lower limit of the atopic range. There were no statistical differences in IgE levels between those patients who were older than 50 years of age and those younger than 50. IgE levels of patients who were taking oral prednisone were lower than those not taking oral steroids, but this did not reach statistical significance (data not shown).

TABLE 3

Percentage of Positive RASTs in the Group of 73 Patients with Asthma

Allergen	Positive RASTS (%)
Dust mite	24
Dog	28
Cat	38
Cockroach	68
Ragweed	17
Grass	15
Tree	14
Aspergillus fumigatus	7

Cockroach, cat, dog, and dust mite were the most common allergens. The mean number of positive RASTs per patient was 2.5.

Prevalence of Positive RASTs among Asthma Patients. Table 3 demonstrates the distribution of positive RASTs in the asthmatic patients. Cockroach was the most common allergen in our study, followed by cat, dog, dust mite, ragweed, trees, grass, and *Aspergillus fumigatus*. There were no positive RAST results in the control group. There was a correlation ($p = 0.04$) between the number of positive RASTs and age less than 50 years (**Fig. 2**).

Discussion

The incidence and severity of asthma, especially in inner-city minority populations, has increased markedly in the past ten years for as yet undetermined reasons (8). Although inadequate asthma treatment and lack of access to proper medical facilities may be influencing this increase in mortality and morbidity, other disease-specific factors may be playing a role as well. Over the past ten years it has become apparent that increases in bronchial airway hyperactivity

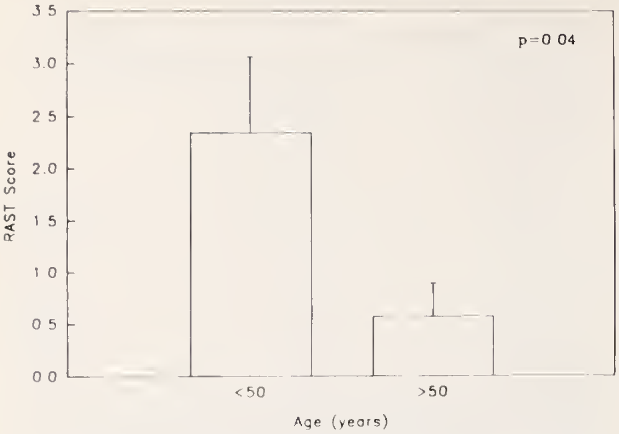

Fig. 2. A statistically significant difference ($p = 0.04$) was demonstrated between the mean number of positive RASTs in asthmatics younger than 50 years of age and in asthmatics older than 50 years.

associated with allergen exposure contribute to both the pathogenesis and severity of asthma (9, 10).

The asthmatic population treated in The Mount Sinai Emergency Room is almost entirely black and Hispanic and predominantly female (64%) (Table 1). Although there is no known sex predisposition for asthma, the predominance of Hispanic and black women observed in our study is similar to the results of Karetzky's study in the South Bronx in 1977 (7). It is uncertain whether this increase in female asthmatics reflects increased severity of disease in black and Hispanic women or increased utilization of emergency room services by this group.

Our asthmatic population appears to have relatively severe disease, as reflected in the amount of medication required to control the asthma, including 22 patients taking corticosteroids (Table 2). Increased severity of asthma is well recognized in inner-city black populations (8) but is less well described in Hispanic groups.

Our data demonstrate that atopy, defined as an elevated IgE level (>100 IU/ml), is extremely common (60% of patients) among asthmatics seen in The Mount Sinai Hospital asthma room. This increase in both total IgE and specific IgE directed against aeroallergens (RAST) appears to be disease specific since it was not found in the age-matched control group. Although IgE levels were higher in the asthmatics younger than 50 years (4–6), this difference did not reach statistical significance. There was, however, a statistically significant association ($p = 0.04$) between the number of positive RASTs and age (under 50 years) demonstrating that specific antiallergen IgE antibodies are more common in younger asthmatics, which is consistent with previous studies (4–6). There was no correlation between either the duration of asthma or the medications needed to control disease and the IgE level or the number of positive RASTs (data not shown). Although 60% of the patients were found to have elevated IgE levels and positive RASTs, no conclusions regarding the role of acute allergen exposure and the asthma that brought the patients to the emergency room can be made. Repeated studies (11–13) have demonstrated that patients generally do not associate allergen exposure with an asthma attack. However, extensive evidence demonstrates that prolonged allergen exposure increases nonspecific bronchial reactivity through the accumulation of inflammatory cells. Neutrophils and eosinophils in the airway may lower the threshold for nonspecific triggers, such as viral infections and exercise, that can provoke acute bronchoconstriction (14–16). The atopic nature of the asthmatic population is similar to other studies performed in rural and suburban populations (4–6).

The asthmatic patients were allergic to an indoor panel of allergens, including cockroach, cat, dog, and dust mite (Table 3). Cockroach was the most common allergen in the asthmatic patients and has been recognized in numerous studies as a major allergen in both allergic rhinitis and asthma (17–19). Cockroach allergens are well characterized (20) and have been demonstrated on bronchoprovocation to induce both immediate and late-phase reactions (20). Although skin-test positivity to cockroach has also been reported by several investigators in diverse groups of asthmatics (21–23), it is especially common among indigent populations of asthmatics usually living in public housing (24). Cockroach and other indoor allergens, especially dust mite, are a perennial source of antigen-inducing airway inflammation. Constant exposure to these allergens may certainly contribute to airway inflammation in this patient population.

In conclusion, elevations in total IgE and specific IgE antibodies directed against an indoor panel of allergens, including cockroach, cat, dog, and dust mite, are present in 60% of the asthmatics seen in The Mount Sinai Hospital asthma room. These allergens are a perennial source of airway inflammation in this population. The atopic component of asthma in these patients must be taken into account in the treatment of this disease, and attempts to reduce airway inflammation by limiting allergen exposure must be utilized.

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Oligoclonal Banding in AIDS and Hemophilia

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Abstract

Hypergammaglobulinemia is a consistent finding in patients within the AIDS spectrum and with hemophilia A. Serum samples from patients with these conditions were analyzed for the presence of oligoclonal banding, using a high-resolution serum protein electrophoresis system. The incidence of banding is significantly greater in well homosexuals who are HIV-antibody positive and in patients with pre–AIDS-related complex, AIDS-related complex, AIDS with opportunistic infections, and AIDS with Kaposi's sarcoma than in normal blood donors. The incidence of banding is similar to controls in patients with hemophilia who have received either no blood products, cryoprecipitate only, or limited infusions of factor VIII concentrate. In patients who have received frequent infusions of factor VIII concentrate, the incidence of banding significantly increases. Thirteen of sixty-seven hemophiliac patients developed AIDS or symptoms related to HIV infection independent of their banding pattern.

We hypothesize that the bands are not diagnostic of AIDS, but seem to correspond with disease progression, and that they are absent early in the disease, appear later in the course, and may disappear with advanced disease.

In the healthy state, immunoglobulins are synthesized by many clones of B cells, in response to the many antigens normally encountered. These normal immunoglobulins can be separated by electrophoresis, and will produce a broad, heterogeneous band in the immunoglobulin region. In some disease states, such as hepatobiliary disease, immunoglobulins originate from the proliferation of one or a few clones of B cells. With electrophoresis, they produce small, discrete bands in the immunoglobulin region called oligoclonal bands. In some disease states, such as multiple myeloma, immunoglobulins originate from the malignant proliferation of a single clone of B cells and produce large dark bands in the immunoglobulin region called monoclonal bands.

Oligoclonal bands have been described in various conditions, including reticular and nonreticular malignancy, infectious disease, hepatobiliary disease, autoimmune disease, heart disease, and AIDS (1–4). In this study we further investigated the incidence and significance of such bands in subjects within the AIDS spectrum and in patients with hemophilia A. We also measured, in some cases serially, the immunoglobulin levels of patients with these illnesses.

Materials and Methods

Serum samples from 224 subjects were analyzed for the presence of oligoclonal bands. The samples were obtained from volunteer blood-bank donors, private ambulatory patients, clinic patients, and hospitalized patients. Some samples were frozen and preserved specimens from the Immunology and Immunochemistry Laboratories of the Mount Sinai Hospital, New York City.

Determination of Immunoglobulin Concentration. Serum concentrations of IgG, IgA, and IgM were measured for each sample by the Beckman automated immunochemistry system (Beckman Instruments, Inc., Brea, CA).

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Electrophoresis. The serum samples were electrophoresed using a high-resolution serum protein electrophoresis, the Beckman Paragon System. The serum samples were diluted to an IgG concentration of 200 mg/dL. A template was placed on an agarose gel, and 4–6 μL of each sample were applied to the gel. The samples were allowed to diffuse for five minutes and then electrophoresed in a barbitol buffer at 100 volts for 40 minutes. The gel was washed in water, fixed in acid-alcohol composed of 20% acetic acid and 30% methanol, dried, stained with Paragon Violet, rinsed in 10% acetic acid, and dried again.

Immunofixation. The bands of 15 subjects were analyzed to determine the immunoglobulin class and light-chain type. Sera were diluted in saline according to their immunoglobulin content to a final concentration of 200 μg/dL for IgG and kappa, 300 μg/dL for lambda, and 100 μg/dL for IgA and IgM. Approximately 4 μL of diluted sera were applied to the appropriate lanes on the agarose gel, allowed to diffuse for five minutes, and then electrophoresed as described above. After electrophoresis, a template was placed on the gel, and antisera to IgG, IgA, IgM, and the kappa and lambda chains were applied to the appropriate lanes. The antisera were allowed to incubate for 15–30 minutes in a humidified chamber. The gels were washed in 0.15 M saline and blotted, stained with Paragon Blue, rinsed in 5% acetic acid, and dried.

Densitometric Scanning. Selected gels were scanned using a Hoeffer densitometer (Model GS300, Hoeffer Scientific Instruments, San Francisco, CA).

Statistical Analysis. The binomial probability distribution was used to determine if the incidence of banding in the patient groups was statistically different from the 5% incidence of banding reported in large control groups (5). Fisher's exact test with a Bonferoni correction for multiple comparisons was used to determine if the incidence of banding was statistically different between patient groups.

Results

Table 1 summarizes the results obtained for controls and for subjects within the AIDS spectrum. None of the 40 normal volunteers had bands, an incidence similar to published normal control values of 5% (5). Sixteen well homosexual men who were HIV-antibody-negative had a banding incidence of 6%, which was not significantly different from the published controls. Thirteen well homosexual men who were antibody positive had a banding incidence of 38%; 12 patients with pre-AIDS-related complex (ARC) (6), here defined as having persistent generalized lymphadenopathy, leukopenia, or thrombocytopenia but not meeting the accepted criteria for ARC, had a banding incidence of 50%; 19 patients with ARC had a banding incidence of 32%; 16 AIDS patients with Kaposi's sarcoma (KS), with or without opportunistic infection, had a banding incidence of 44%; and 41 AIDS patients with opportunistic infections (OI) had a banding incidence of only 15%. All of these groups were significantly different from the controls ($P < 0.01$). **Fig. 1** shows a sample from a patient with ARC, demonstrating three bands.

TABLE 1

Oligoclonal Banding in Control Subjects and Patients within the AIDS Spectrum

Diagnosis	N	No. with bands (%)	Total no. of bands	*P*	Mean IgG (g/dL)	Risk group	No. with bands/N
Controls							
Volunteer blood donors	40	0 (0)	0	0.87*	1050 ± 210		
AIDS-spectrum Subjects							
Well homosexuals							
HIV-Ab negative	16	1 (6)	1	0.37	1020 ± 230	All homosexual	1/16
HIV-Ab positive	13	5 (38)	7	<0.01	1645 ± 520	All homosexual	5/13
PreARC	12	6 (50)	10	<0.01	2250 ± 859	Homosexual	5/9
						IVDA	1/3
ARC	19	6 (32)	8	<0.01	2250 ± 1308	Homosexual	1/13
						IVDA	4/6
AIDS:KS	16	7 (44)	14	<0.01	3080 ± 1355	Homosexual	3/21
						Unknown	2/12
AIDS:OI	41	6 (15)	12	0.01	1850 ± 575	Homosexual	3/21
						IVDA-related	1/8

IVDA, intravenous drug abuser; OI, opportunistic infections; KS, Kaposi's sarcoma.

* All groups are compared to a published normal control value of 5% (4).

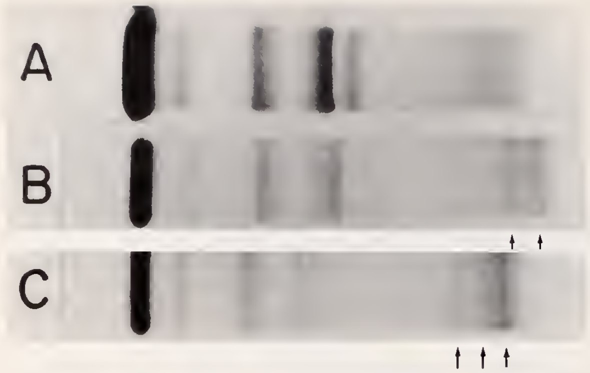

Fig. 1. Lane A: Normal control. Lane B: Hemophilia patient treated with large amount of F VIII; 2 bands. Lane C: ARC, IVDA; 3 bands.

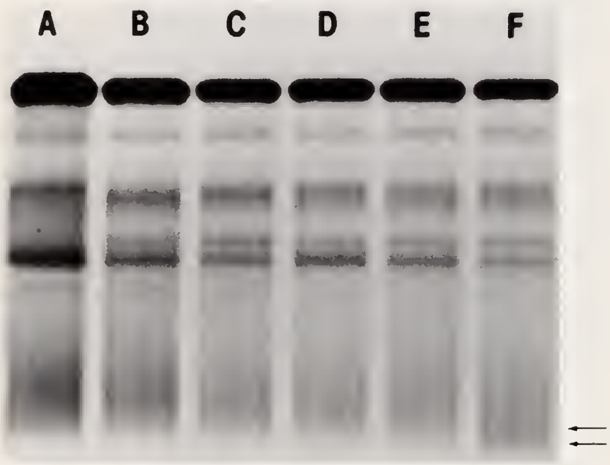

Fig. 3. Development of bands over time in hemophilia patient treated with large amounts of F VIII. Lanes A–E: 1978–1982; 0 bands. Lane F: 1984; 2 bands.

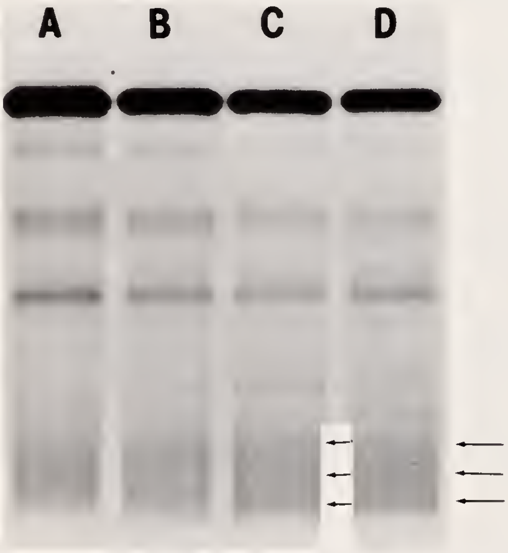

Fig. 4. Development of bands over time in hemophilia patient treated with large amounts of F VIII. Lane A: 03/83; 0 bands. Lane B: 08/83; 0 bands. Lane C: 10/84; 3 faint bands. Land D: 05/85; 3 distinct bands.

The incidence of banding between patient groups did not reach statistical significance using Fisher's exact test with a Bonferoni correction, which would require a *P* of 0.01 to be significant. However, a trend toward significance was suggested between AIDS with OI and AIDS with KS ($P = 0.03$) and between AIDS with OI and preARC ($P = 0.02$).

Mean IgG levels (Table 1) were: controls, 1050 mg/dL; well homosexual antibody-negative, 1020 mg/dL; well homosexual antibody-positive, 1645 mg/dL; preARC, 2250 mg/dL; AIDS with OI, 1850 mg/dL; and AIDS with KS, 3000 mg/dL.

Serial IgG levels were available for 13 of 41 patients who had AIDS with OI (Fig. 2), and these were analyzed for changes in IgG level. A change in IgG level is defined here as greater than 100 mg/dL. Seven patients had decreasing IgG levels, one had increasing, then decreasing IgG levels, 2 had stable levels, and 3 had increasing levels.

In the hemophilia group (**Table 2**), no banding was seen in nine patients who had never been treated with factor VIII concentrate (F VIII), though they may have been treated with cryoprecipitate. No banding was seen in five patients who had been treated with fewer than 10 infusions of F VIII. In patients treated with large amounts of F VIII (10 infusions or more), the incidence of banding was 50%, which was statistically different from controls ($P < 0.01$). In patients with hemophilia who developed AIDS, the incidence of banding was 23%, not statistically different from controls. Fig. 1 shows a sample from a patient with hemophilia treated with large amounts of F VIII, demonstrating two bands.

In several patients treated with large amounts of F VIII, the development of multiple bands occurred over time, presumably related to increased amounts of F VIII infused. Serial samples of patients treated with large amounts of F VIII (**Figs. 3, 4**) show the development of increased numbers and intensity of bands over time.

Mean IgG levels in study subjects tended to increase with increased use of F VIII:

- no F VIII or cryoprecipitate only: 1190 mg/dL
- treated with F VIII <10 times: 2020 mg/dL
- treated with F VIII ≧10 times: 2070 mg/dL
- treated with F VIII ≧10 times and developed AIDS: 2510 mg/dL

Serial IgG levels were available in 3 of the 4 hemophiliac patients who developed AIDS (**Fig. 5**). All three patients had initially rising and subsequently falling IgG levels. There was no change

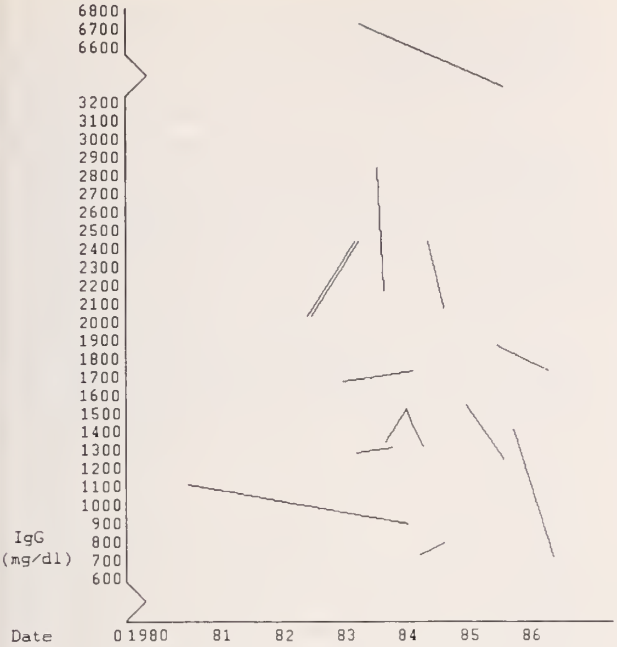

Fig. 2. Changes in IgG over time in 13 patients who had AIDS with opportunistic infections.

in the banding pattern of one hemophiliac AIDS patient as the IgG level decreased.

Immunofixation was performed on the sera of eight patients in the AIDS group who had a total of 13 bands. Six bands were IgG kappa and IgG lambda and seven were IgG kappa only.

Immunofixation was performed on the sera of seven patients in the hemophiliac group who had a total of 12 bands. Five bands were IgG kappa and IgG lambda, and seven were IgG kappa only.

Discussion

The absence of banding in our controls and the 6% incidence in well homosexual men who are HIV-antibody-negative are similar to the incidence reported in normal controls (1). The banding incidence is 30%–50% in well antibody-positive male homosexuals, and patients who have preARC, ARC, and AIDS with KS, whereas it is 15% in AIDS with OI. The 15% incidence in patients who have AIDS with OI is similar to that reported by Papadopoulos et al.; the 44% incidence in patients who have AIDS with KS is somewhat lower than in that series (2). The incidence of banding was significantly less in the AIDS with OI group than in well, antibody-positive homosexual men and patients who have preARC, ARC, and AIDS with KS. The IgG data of patients with AIDS with OI show that a decreasing IgG level is often present; 8 of 13 patients studied serially had decreasing levels of this immunoglobulin. Both the decreased frequency of banding and the decreasing IgG levels suggest a progressive B-cell dysfunction as one progresses within the AIDS spectrum to opportunistic infection.

In patients with hemophilia A treated with large amounts of F VIII, the incidence of banding is 50%. The development of multiple bands is shown to occur over time in several patients, presumably related to increased amounts of F VIII used for treatment. The presence of banding, however, does not seem to correlate with clinical status. Among patients treated with large amounts of F VIII, 4 of 24 with banding have signs or symptoms which could fall within the AIDS spectrum, including persistent generalized lymphadenopathy, fever, weight loss, or idiopathic thrombocytopenic purpura. Five of 24 patients without banding have similar signs of symptoms. The other 39 patients treated with large amounts of F VIII are clinically well, except for hemophilia.

TABLE 2
Oligoclonal Banding in Hemophilia A

Subgroup	N	No. with bands (%)	Total no. of bands	*P*	Mean IgG (mg/dL)
Controls n = 40					
Volunteer blood donors	40	0 (0)	0	0.87*	1050 ± 210
Hemophiliac Subjects n = 67					
Cryo only	9	0 (0)	0	0.63	1190 ± 360
F VIII (<10 infusions)	5	0 (0)	0	0.77	1930 ± 410
F VIII (10 infusions)	49	24 (50)	45	<0.01	2105 ± 805
Developed AIDS	4	1 (25)	2	0.17	2510 ± 950

Cryo, cryoprecipitate. F VIII, factor VIII.
* All subgroups are compared to a published normal control value of 5% (4).

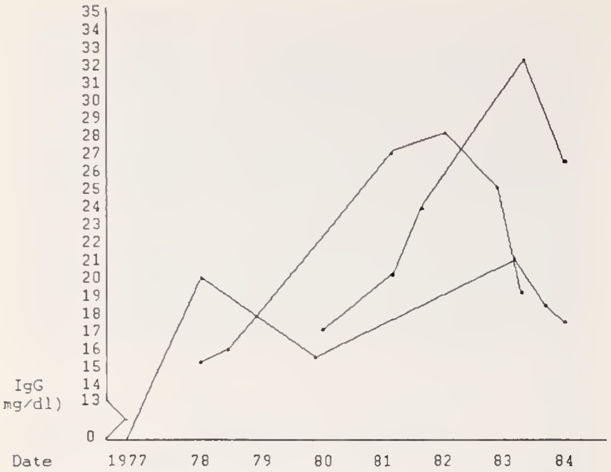

Fig. 5. Changes in IgG over time in 3 of 4 hemophilia patients who developed AIDS.

Only one of 4 patients with hemophilia who developed AIDS had banding. Again, there was a suggestion that decreasing IgG levels might be associated with deteriorating clinical status. In 3 patients who developed AIDS and in whom serial samples were available, the IgG levels initially increased, and then later decreased.

It has been previously shown by Lane et al (5) that patients with AIDS have abnormal B-cell function. They have an increased number of B cells which spontaneously secrete immunoglobulin, and this finding is more pronounced in patients with KS than in those with OI. AIDS patients also have an abnormally reduced B-cell proliferative response to mitogens and to new antigens. In another study, Lane et al. showed that patients with OI are more immunosuppressed than patients with KS (7), as judged by lower numbers of total lymphocytes, T lymphocytes, and B lymphocytes, and decreased proliferative responses to mitogen (4).

Amadori and Chieco-Bianchi have also summarized B-cell abnormalities in HIV infection (8–14). B cells are activated in large numbers and secrete large amounts of immunoglobulin. Some of the immunoglobulin is polyclonal and directed against a variety of antigens, but memory B lymphocytes do not appear to function normally. Much of the secreted immunoglobulin, however, is directed against the HIV virus itself, and is felt to be the origin of the oligoclonal and monoclonal bands seen in the serum and cerebrospinal fluid of these patients. Amadori hypothesizes that these antibodies may be involved in the pathogenesis of immune damage seen in HIV-infected patients by enhancing infectivity, by promoting complement and cell-mediated damage to infected and bystander cells, and by promoting lymphoma development.

The observations we have made are compatible with the findings of Lane and Amadori and are compatible with, but do not prove, the following sequence of events. HIV-infected individuals, including patients within the AIDS spectrum and patients with hemophilia treated with frequent F VIII infusions (presumably 95% of whom are HIV-antibody positive) are exposed to a variety of antigens early in the disease. These patients are initially able to respond appropriately and produce immunoglobulins with the aid of T lymphocytes. As the disease progresses somewhat, there is ongoing antigenic stimulation with both regulated and spontaneous secretion of immunoglobulins, leading to hypergammaglobulinemia, increased anti-HIV antibodies, and increased likelihood of oligoclonal banding. As the disease progresses even further, the patients develop more advanced immunodeficiency, with decreasing immunoglobulin levels and decreased oligoclonal banding. This last stage may be due to a profound loss of helper-inducer T lymphocytes, necessary for B-cell function, or to an intrinsic dysfunction of the B lymphocyte itself. Furthermore, OI may ensue most easily in those who have progressed to this most advanced stage of B-cell and T-cell immunodeficiency.

Thus, the evaluation of oligoclonal banding in AIDS and hemophilia may provide another insight into the immune dysfunction of HIV disease. The bands are not diagnostic of AIDS, as they are present in several other conditions, but seem to correspond with the status of disease progression. They are absent early in the disease, appear later in the course, and may disappear as the disease becomes quite advanced.

Acknowledgments

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Gold-Induced Colitis:

A Case Report and Review of the Literature

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Abstract

A case of severe colitis requiring subtotal colectomy following administration of 35 mg Solganal b for intractable arthritis is described. Abdominal pain and watery diarrhea developed six weeks after the last dose of gold. Colonoscopy revealed mucosal edema and ulceration of the entire colon. Supportive measures failed and the patient required subtotal colectomy. Review of the literature revealed 29 cases, ranging in severity from limited ileal involvement to fulminant panenteritis. Most of the patients responded to intravenous fluids, steroids, and antibiotics, but four required surgery. The case described is notable for the delay in appearance of abdominal symptoms following the cessation of gold therapy. The mechanism of injury is unknown. Abdominal complaints in a patient who has received gold therapy, especially parenteral, merit strict attention, even if occurring several weeks after the final dose, and the diagnosis of gold colitis should be entertained.

Most physicians using gold therapy to treat patients with rheumatoid arthritis are aware of the significant incidence of toxicity, ranging from 25% to 50% (1). Cutaneous reactions are the most common, but blood dyscrasias and proximal tubular damage may also occur, requiring regular examination of the skin, blood, and urine during treatment. Gastrointestinal complications other than nausea and vomiting are extremely rare, however; only 29 cases of gold enteritis have been previously reported.

We describe a patient who developed severe colitis after administration of gold for intractable rheumatoid arthritis and who ultimately required subtotal colectomy.

Case Report

A 56-year-old woman was diagnosed with seronegative rheumatoid arthritis six years ago. Three months prior to admission, she had been started on weekly gold injections for intractable arthritis. After two injections, totaling 35 mg, she developed a rash over her legs. The gold therapy was discontinued and the rash improved with topical steroids. Six weeks later, however, she developed fever, abdominal pain, and diarrhea, requiring hospitalization. The pain was distributed diffusely over the lower abdomen and relieved by defecation. The diarrhea occurred 10–15 times a day, was watery to semisolid, and bloody on some occasions. On colonoscopy, the mucosa was edematous, granular, and friable throughout the entire colon; cobblestoning and linear ulcers were also noted. Biopsy revealed severe acute colitis with many crypt abscesses and mucin depletion. The patient was given intravenous steroids for three weeks with no improvement. She was then transferred to The Mount Sinai Hospital.

On examination, she appeared ill, and had a pulse rate of 120/min, blood pressure of 90/60 mmHg, temperature of 100°F, and mild pedal edema. An erythematous, macular, scaly rash was distributed mainly over her back and arms. Thrush was noted within the oral cavity. The abdomen was distended and diffusely tender with diminished bowel sounds.

Laboratory data were as follows: The hemo-

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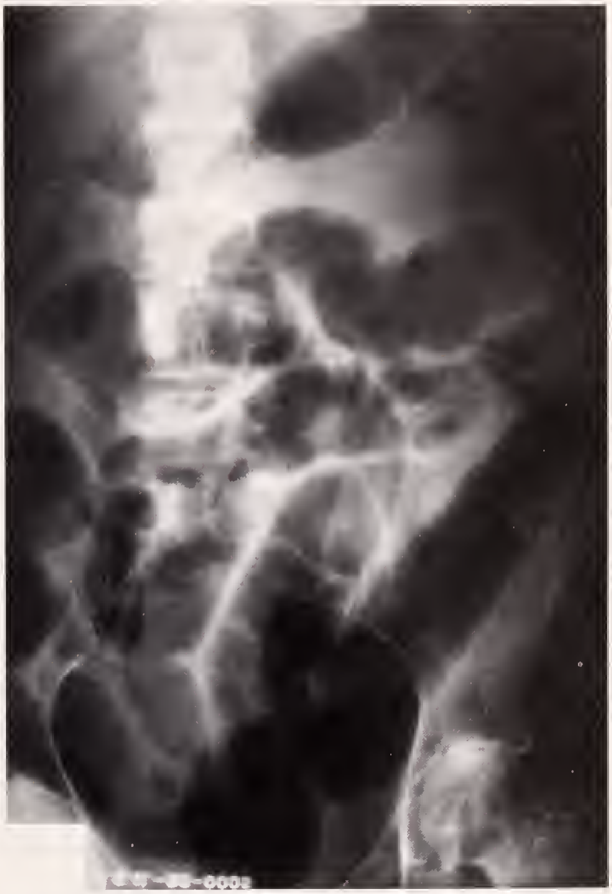
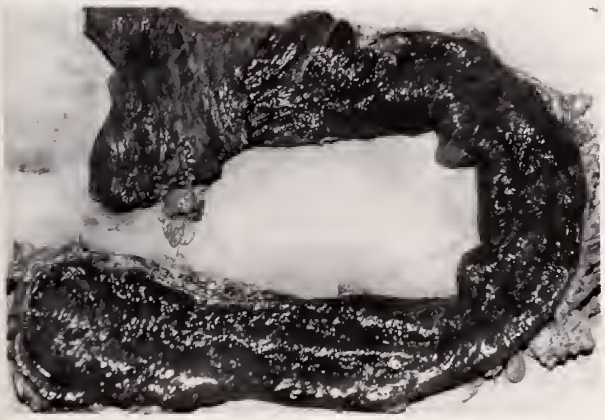
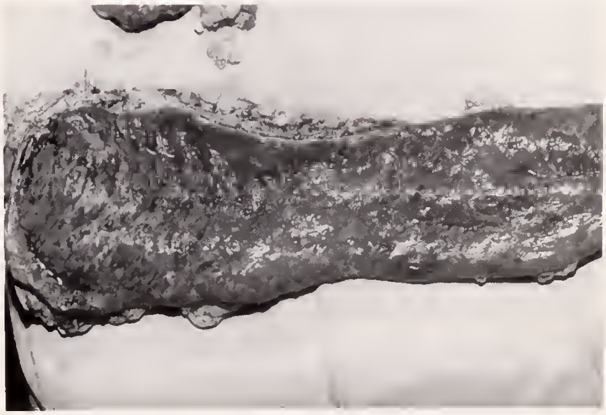


Fig. 1. Right Abdominal films revealing dilated edematous small bowel in midabdomen and loss of haustral markings in sigmoid colon. **Fig. 2. Below left** Subtotal colonic resection specimen showing active universal ulcerative colitis. **Fig. 3. Below right** Closer view showing marked edema, granular mucosa, and linear ulcers.





globin was 8 g/dL and hematocrit 23.4%; white blood cell count 8200/mm with 23% neutrophils, 50% band forms, 25% lymphocytes, and 2% monocytes. Erythrocyte sedimentation rate was elevated to 72 mm/hr. Prothrombin time was normal. Serum sodium was 117 mEq/L, potassium 4.4 mEq/L, chloride 95 mEq/L, CO_2 19 mEq/L, BUN 13 mg/dL. Total protein was decreased to 3.2 g/dL, with serum albumin only 1.2 g/dL. Bilirubin was 4.2 mg/dL and amylase 142 I units/mL; all other liver function tests were normal. An abdominal X-ray revealed dilated loops of large and small bowel (**Fig. 1**).

Her condition continued to deteriorate, and two days after transfer she underwent subtotal colectomy and Brooke ileostomy (**Figs. 2, 3**). At the time of operation, the entire intraabdominal colon was inflamed and edematous, but the terminal ileum and rectum appeared normal.

Postoperatively, the patient developed some melena. Upper gastrointestinal endoscopy showed two ulcers, one in the pyloric region and another on the lesser curvature of the stomach. She was treated with cimetidine. The remainder of her hospital stay was unremarkable; approximately 1½ months after admission, she was discharged. She was readmitted six months later for elective ileorectal anastomosis and has remained well over the next 3½ years of follow-up.

Discussion

In 1935, Goldhammer described a 47-year-old woman who developed severe diarrhea after receiving a total dose of 240 mg Solganal b for primary chronic polyarthritis. The patient died after 12 days despite supportive therapy. Autopsy showed severe mucosal edema and hemorrhage throughout the small and large bowel (3). Since then, 29 cases of gold-induced enterocolitis, including this one, have been described.

Most of these patients, like this one, have been middle-aged women, but this observation probably reflects the greater prevalence of rheumatoid arthritis in this group rather than an inherent susceptibility.

Our case was unusual in three respects. First, six weeks had elapsed after the cessation of gold therapy before the onset of abdominal complaints. In most cases, enterocolitis occurs early in the course of treatment. All patients described had received 510 mg or less, except for one who had received two cycles totaling 3,200 mg before enterocolitis developed (15).

Second, at the time of transfer, the patient still had the skin rash that had been her initial symptom. Only four reported cases had other signs or symptoms of gold toxicity accompanying their enterocolitis (3, 8, 11, 12).

Third, the need for colectomy was unusual. Although 6 of the 12 patients described up to 1976 died (3–12), only 2 of the 17 patients subsequently reported on have died (13–27). Only three patients required colectomy, two for perforation (15, 18). One survivor underwent diversion with a loop ileostomy (26).

The mechanism of gold-induced bowel injury is currently unknown. Although nearly all patients received parenteral therapy, one case did occur in a patient taking auranofin, an oral compound. Thus, a direct toxic effect on the intestinal mucosa related to the drug's high rate of fecal excretion may be the inciting event (2). Two patients, however, both of whom died, had a history of bloody diarrhea (7, 9); in these patients, gold therapy may have exacerbated previously existing disease. In all reported cases, the joint disease was characteristic of rheumatoid arthritis and not suggestive of colitic arthritis. In all previously reported cases, stool examination was performed and no pathogens were identified. Small-bowel series have revealed rapid transit time (9, 13, 20) or mucosal thickening (8, 11). Barium enemas have shown colonic spasticity (3), edematous mucosa (9, 14, 22), or a normal appearance (10, 11, 19, 20). Involvement ranged from ileum only (7) to fulminant panenteritis (5, 8, 18). Pathologic changes included edematous mucosa, ulcerations, and hemorrhages with infiltration of lymphocytes, plasma cells, and polymorphonuclear lymphocytes (3, 5, 9–19, 21–23). One of the patients described by Fam et al. also had thrombosis of several mucosal vessels, identified on histologic review (15).

Alternatively, the mechanism of injury may be an immune-mediated response. In support of this theory, Szpak et al. demonstrated marked tritiated thymidine uptake following mixed lymphocyte stimulation with gold sodium thiomalate in the patient they described, a phenomenon not seen in normal controls or arthritic patients receiving gold therapy without evidence of toxicity (13). In addition, Wright et al. demonstrated circulating immune complexes in their patient, which were cleared following the resolution of colitis (25). A delayed immune response rather than direct mucosal toxicity may account for the six-week lag in onset of abdominal symptoms and the persistent rash in our patient.

In any case, early diagnosis is mandatory. The onset of diarrhea in a patient receiving or who recently received parenteral gold should alert the physician to the possibility of this complication. Aggressive investigation to determine the cause should be instituted and gold therapy discontinued immediately, if it has not been already. Most patients will improve with adequate fluid replacement and administration of steroids and antibiotics. If this regimen fails, colectomy may be required. In contrast, patients receiving gold orally will frequently experience mild diarrhea or other gastrointestinal symptoms. Such responses in these patients require downward adjustment of the dose and close follow-up.

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Progressive Nemaline Rod Myopathy in a Woman Coinfected with HIV-1 and HTLV-2

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Abstract

Nemaline-rod myopathy was recently reported in eight young males infected with human immune deficiency virus type 1 (HIV-1). A 41-year-old woman had a 2-year history of progressive proximal-muscle weakness. Muscle biopsy demonstrated the presence of nemaline rods, predominantly in type 1 fibers. She was coinfected with HIV-1 and HTLV-2, as evidenced by positive polymerase chain reaction and serology. There was no lymphopenia or CD4 lymphopenia, despite an abnormal T-cell subset ratio, high CD8 count, skin anergy, and depressed in vitro response to mitogens. This case raises the possibility that dual infection may play a role in the pathogenesis of the rare nemaline-rod myopathies of HIV-infected patients.

SKELETAL-MUSCLE DISEASE associated with human immunodeficiency virus type 1 (HIV-1) infection has recently been reported. Most reported cases confirmed by muscle biopsy exhibit inflammation as seen in polymyositis; others show features of necrosis and regeneration without concurrent cellular infiltrates, but have nonetheless been considered inflammatory in origin (1–4). In addition, over the last four years, eight cases, all young males infected with HIV-1, have been reported with progressive proximal weakness; in all the predominant finding on muscle biopsy was the presence of nemaline rods (4–8). We report the case of a young woman with severe progressive proximal weakness, coinfected with HIV-1 and human T-cell lymphotropic virus 2 (HTLV-2), in whom a nemaline-rod myopathy was seen on biopsy.

Case Report

In June 1990 a 41-year-old U.S.-born black woman consulted a physician for a 2-year history of progressive weakness which began with difficulty climbing stairs and getting off a toilet seat and was followed by proximal upper-extremity weakness six months later. She reported some intermittent, pruritic nodular lesions on her legs. She had had dermatomal herpes zoster in October 1989. One relevant element in her history was that she had been a high-school track star. Both her parents, eight siblings, and four children have no evidence of neuromuscular problems. Her husband, an intravenous-drug user, had died of AIDS in September 1988. She had not received blood transfusions or used illicit drugs.

She had a markedly waddling gait with prominent lumbar lordosis and was unable to rise from a chair. There was bilateral and symmetrical weakness of the neck flexors (4/5); deltoid, supraspinatus and infraspinatus (2/5); biceps, triceps, and wrist extensors (3/5); finger flexors and intrinsic hand muscles (4/5); iliopsoas (1/5), quad-

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riceps, hamstrings, and glutei (2/5); and all muscles distal to the knees (5 – /5). All deep tendon reflexes were absent except the ankle jerks, which were 2+. The general physical examination was negative; in particular, lymphadenopathy, splenomegaly, and oral abnormalities were absent.

Creatinine kinase (CK) was normal (<190 IU/L) on five separate occasions. The ESR was 98 mm/hr. Antibodies tested for HIV-1 by enzyme-linked immunoadsorbent assay (ELISA) and Western blotting were positive (**Table 1**). Peptide ELISA for HTLV-1 and HTLV-2 were positive, but the reactivity was far stronger to HTLV-2 peptides than to those derived from HTLV-1, with which there is a known cross-reactivity. The presence of both HTLV and HIV-1 proviruses was confirmed by the polymerase chain reaction (PCR), using probes for HIV-1 gag (6500 copies/10^6 cells), HTLV-1/2 pol SK115, and HTLV-2 pol SK188; the HTLV-1–specific pol SK112 probe did not react on PCR.

These results, combined with the serologic findings on peptide ELISA, suggest that the patient is infected with HTLV-2 and HIV-1. Direct cocultures of the patient's cells with PHA-stimulated normal cells for HIV-1, using HIV-1 p24 antigen as the culture endpoint, were negative through 27 days. The patient was anergic to a battery of seven common recall antigens in delayed-type hypersensitivity (Multitest-CMI, Merieux Institute USA, Miami, FL).

Electromyographic analysis of the motor-unit potentials of one vastus medialis, anterior tibialis, and the biceps brachii muscle revealed decreased mean durations, reduced amplitudes, and minimal polyphasia. Muscle biopsy was obtained from the opposite vastus medialis. Hematoxylin- and eosin-stained sections showed a highly abnormal muscle with marked variation in fiber diameter (range 5–140 micron). Large fibers were oval to rounded. Internal nuclei were markedly increased in size. Atrophic rounded or wedged fibers were noted singly and in small groups. Increased fibrous tissue was present around atrophic fibers. Atrophic fibers with nuclear clumps were present. Scattered fibers showed vacuolation and granular degeneration. A few small endomysial, perimysial, and epimysial vessels showed light lymphoplasmacytic cuffing. Muscle trichrome stain revealed numerous aggregates of nemaline rods mainly within atrophic fibers. Enzyme histochemistry (ATPase) revealed that nemaline rods were present mainly in type 1 fibers, although type 2 fibers were also involved to a lesser degree. Electromicroscopy showed the presence of nemaline rods in varying profusion, mostly in atrophic fibers, together with Z-band streaming, myofilament loss, and disorganization (**Fig.**).

Discussion

Over the last four years, eight cases of nemaline-rod myopathy have been reported in association with HIV-1 infection, all in young males with a history of progressive proximal-muscle weakness (4–8) (**Table 2**). In our patient a nemaline-rod myopathy occurred in association with coinfection by HIV-1 and HTLV-2, thus raising the possibility that dual infection may play a role in its pathogenesis.

In all reported cases, including ours, the electrophysiologic studies were consistent with a myopathy. Creatinine kinase levels were mildly elevated in 5 patients, within normal limits in 3, and not available in one (Table 2). Helper-suppressor ratio was abnormally low in 3 patients (6), as in the case reported here, normal in 1 (6), and not reported in 4 patients. CD4 counts were reported in 3 patients and varied from 951 mm^3, in our patient, to 540 mm^3 and 560 mm^3. HTLV-infection status was not evaluated in the other cases. Of the 8 patients with nemaline-rod myopathy so far reported, 5 had not developed any HIV-related symptoms (4–6). Two others had AIDS-related complex (ARC) (4, 8), and only one exhibited fully developed AIDS (7) (Table 2).

The most striking histologic finding on muscle is the diffuse presence of nemaline rods; in five cases, including ours, these rods were predomi-

TABLE 1

Summary of Patient's Immune Function Tests

Test	Results
Absolute lymphocyte count	2,438 cells/mm^3
CD4 count	951 cells/mm^3 (39%)
CD8 count	1,329/mm^3 (54%)
CD4:CD8 ratio	0.72
Lymphocyte proliferation without added mitogen	1809 cpm (elevated)
Response to phytohemagglutinin	18,037 cpm (depressed)
Response to pokeweed mitogen	1,872 cpm (depressed)
Response to concanavalis A	12,861 cpm (normal)
Natural killer cell activity against K562 target cells	depressed
Antibodies to rapid plasma reagin (RPR)	not detectable
ELISA for cytomegalovirus and toxoplasma	positive
Rheumatoid factors (serum dilution of 1/20)	present
Antinuclear antibodies (ANA)	negative

TABLE 2
Findings in 9 Patients with HIV-Associated Nemaline Myopathy

Patient age/sex/ref	Risk factor	Associated condition	Clinical signs	CPK (IU/L)	Muscle biopsy		Treatment & course
					Inflammation	Nemaline rods	
26/M/5	H	HIV$^+$	PMW	480 (↑)	0	+ Predominantly type I fibers	Not treated Slow progression of weakness and wasting (14 mo)
26/M/6	H	HIV$^+$	PMW upper > lower	752 (↑)	0	+ Predominantly type I fibers	Pred; clinical improvement (6 mo)
29/M/6	Bisexual	HIV$^+$	PMW upper > lower	900 (↑)	0	+ Predominantly type I fibers	Plasmaphoresis; minimal improvement
32/M/4	H	ARC	PMW decreased reflexes	543 (↑)	0	+	Pred; improved for 2 yr.; relapsed; pred. increased
45/M/4	H	HIV$^+$	PMW	260 (NL)	Severe	+	Pred for 2 yr; improved; normal and off medication (5 yr)
40/M/4	H	HIV$^+$	PMW	Not Avail.	0	+	Pred; improved (3 yr) spontaneous improvement (4 mo)
34/M/7	Unknown	AIDS	PMW, dysphagia	210 (NL)	0	+	Retrovir for AIDS; when PMW developed, interferon alpha was added; some improvement (2 yr)
24/M/8	IVDA	ARC	PMW	313 (↑)	0	+ Predominantly type I fibers	Not treated Progressive deterioration (6 mo)
41/F/ present case	Husband IVDA Died from AIDS	HIV$^+$ HTLV-2$^+$	PMW	142 (NL)	0	+ Predominantly type I fibers	Not treated Stable (20 mo)

CPK, creatine phosphokinase; H, homosexual; AIDS, acquired immunodeficiency syndrome; ARC, AIDS-related complex; PMW, proximal muscle weakness; Pred, prednisone; IVDA, intravenous drug abuse; +, positive.

nantly present in the type 1 fibers (5, 6, 8). Necrosis and loss of sarcomeric thick filaments have also been reported in most cases. Inflammatory infiltrates were conspicuously absent in 6 patients (including the present case), mild in 2, and moderate to severe in one (4).

Nemaline rods originate in the Z bands (9), and their constituents are actin and alpha-actin, the protein through which actin filaments are attached to the Z bands. They are the result of a nonspecific myofibrillar alteration resulting from Z-band disorganization and disruption. Rod bodies were first described in congenital nemaline (rod body) myopathy (10). Adult-onset nemaline myopathy (11) has also been described. Nemaline rods have also been reported in other disorders, including mitochondrial myopathies (12) and polymyositis (13).

The pathogenesis of nemaline rods in HIV-related myopathy is not known; the finding of inflammatory changes, severe in one patient and mild in 2 (4), may link these patients with those in whom the myopathy is clearly inflammatory and in whom nemaline rods were not found. Simpson and Bender (4) comment that a low degree of inflammatory response may be related to T- and B-cell abnormalities. It is possible that all the myopathic variations in HIV infection reflect a spectrum of the same disease, predominance of nemaline rods being at one extreme and predominance of inflammatory infiltrates at the other (4, 8).

The finding of progressive nemaline (rod) myopathy as the only clinical manifestation reported in some HIV-related myopathies—with complete failure to demonstrate or cultivate the virus from muscle specimens using a variety of techniques, including electronmicroscopy—suggests that retrovirus can indirectly, by means of immunopathologic mechanisms, affect the primary structural and contractile proteins of the muscles (5). It is possible that this HIV-associated myopathy is produced by an autoimmune mechanism; autoimmune thrombocytopenic purpura and chronic inflammatory neuropathy are examples of disorders considered to be autoimmune that occur in association with HIV infection (14, 15). In support of this hypothesis is the improvement of the symptoms with corticosteroid in 4 patients (4, 6) and plasmapheresis in 1 (6) (Table 2). On the other hand, Wiley et al. (16) postulated direct infection of muscle fibers by HTLV-1 in a patient who had polymyositis and was doubly infected with HTLV-1 and HIV. Ishii et al. (17) reported the isolation of HTLV-1 from a patient with polymyositis. Further studies are required to elucidate the pathogenesis of these retrovirus-associated myopathies.

In the patient reported on here, the clinical significance of the coinfection with HIV-1 and HTLV-2 in causing the myopathy is not clear. The spectrum of HTLV-1–associated neurologic disease is restricted mostly to the tropical spastic paraparesis syndrome (18) and to a few cases of polymyositis (16, 17). No neurologic syndrome related to HTLV-2 has yet been described, although a few sporadic cases of central nervous system disorders, for example cerebral lymphoma, subacute encephalitis (19), uveomeningoencephalitis (20), and dementia with frontal lobe syndrome (21), were reported in HTLV-2–positive patients. Recently, a case of a patient infected with HTLV-2 has been associated with a tropical spastic paraparesis-like illness (22).

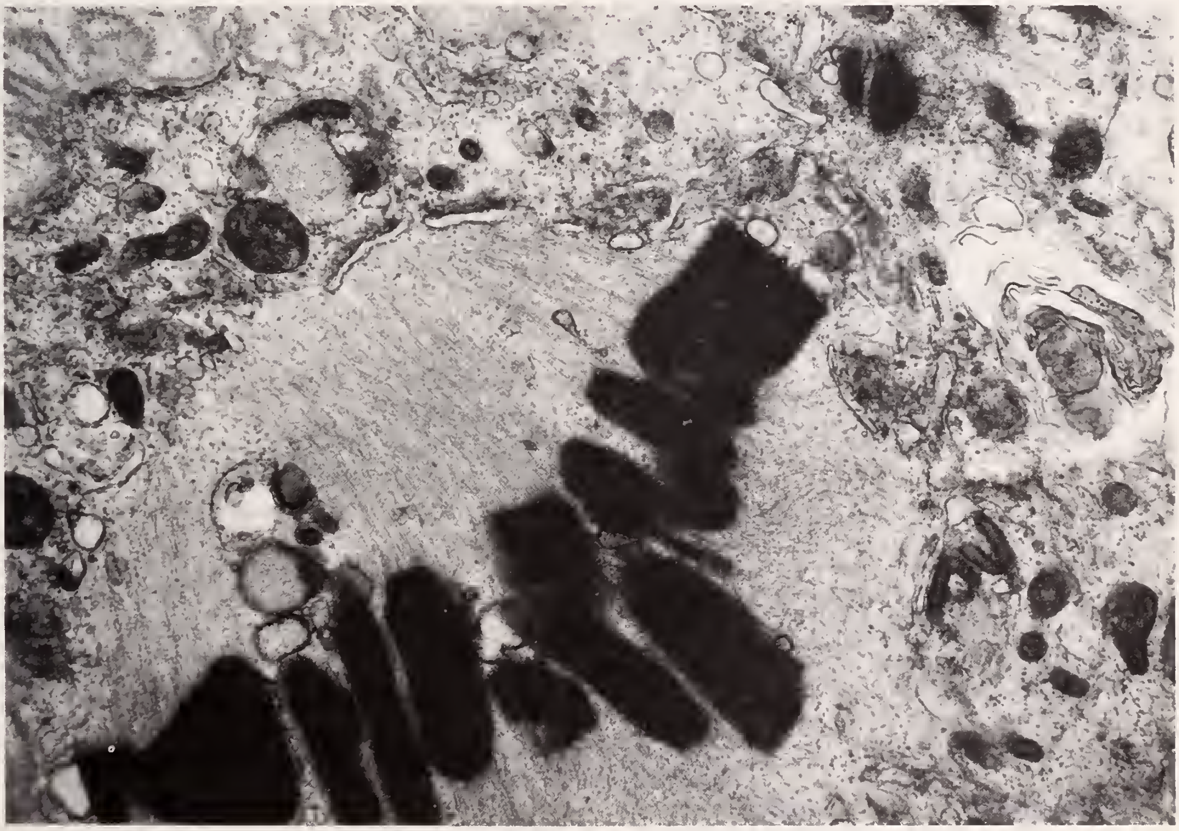

Fig. Electron micrograph of nemaline rods in 41-year-old woman coinfected with HIV-1 and HTLV-2 (original magnification ×17,500).

In the case reported here, the relevance of the disturbances in cellular immunity (CD8 lymphocytosis with abnormal T-cell subset ratio) to her initial clinical symptoms and myopathic findings is also uncertain. It is possible that high CD8 counts are involved in the pathogenesis of this patient's myopathy. The possible role of polyclonal or perhaps even monoclonal myocytotoxic T cells in the myopathic process clearly deserves further evaluation.

This case suggests that serologic surveys of primary myopathies in HIV infection for the presence of the other known human retroviruses (HTLV-1 or -2) should be performed; it is possible that dual infection is a necessary pathogenetic factor.

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Abstracts

The abstracts whose titles and authors are presented here—all authors are principal investigators in the Samuel Bronfman Department of Medicine of the Mount Sinai School of Medicine, which includes the affiliates Beth Israel Medical Center, the Bronx Veterans Administration Medical Center, and Elmhurst Hospital Center, in New York City—were exhibited with the abstract texts as posters in the Department of Medicine Tenth Annual Research Day, November 17, 1992.

Six abstracts by students, fellows, and house staff working in the Department of Medicine received Tenth Annual Department of Medicine Research Awards and were presented orally at a Special Grand Rounds the same day; these are identified by asterisks.

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Abstracts

These abstracts summarize research in ophthalmology by investigators working at Mount Sinai School of Medicine (CUNY) in New York City. They are part of the 1993 Association for Research in Vision and Ophthalmology abstracts and are published here concurrently with publication in Investigative Ophthalmology.

Abstracts in Ophthalmology from Mount Sinai Medical Center 1993

Alpha-Adrenergic Antagonists: Effects on Aqueous Humor Dynamics in the Rabbit and Monkey Eye. T. Taniguchi†, S. M. Podos† and T. W. Mittag†*. Depts. of Ophthalmology† and Pharmacology*, Mount Sinai School of Medicine, New York, NY.

Purpose. Some α_1-adrenergic antagonists such as prazosin are modest ocular hypotensive agents, but their mechanism(s) of action is uncertain. Recent cloning studies show three mammalian α_1 receptor subtypes, A, B and C. Prazosin has highest affinity at α_1 A and α_1 B receptors. As yet there are no highly subtype-selective α_1 antagonists. We have investigated the α_1-antagonist BE2254 (BE), which has high affinity binding sites in rabbit ciliary processes consistent with α_1 C receptors. *Methods and Results.* Topical BE (0.2–0.5%) lowered IOP in rabbit and in normal and glaucomatous monkey eyes by 4–8 mmHg from 1 hr to 6 hours after treatment. At 1 hr after 0.5% BE, rabbit outflow facility measured tonographically (untreated 0.28 ± 0.07 (S.D.); treated 0.29 ± 0.07, n = 8) or by two-level constant pressure perfusion (untreated 0.18 ± 0.010; treated 0.19 ± 0.011) was unchanged. Uveoscleral outflow, determined at 1–1.5 hrs post-BE by fluorescein-dextran perfusion in rabbit eyes, showed no significant drug effect (saline-treated 0.29 ± 0.05, untreated eye 0.27 ± 0.10, drug-treated eye 0.31 ± 0.08 μl/min at 15 mmHg). However, aqueous humor formation measured fluorophotometrically was significantly ($p < 0.05$) decreased in rabbit eyes over a 3 hr period after 0.5% BE treatment (baseline 2.47 ± 0.60, treated 1.85 ± 0.53 μl/min). *Conclusions.* These results suggest that aqueous humor formation by ciliary processes is modulated by α_1 C adrenergic receptors in addition to the well-known responses to α_2 and β_2 adrenergic receptor drugs.

Antidepressants and an H_1 Blocker Reduce Cl Transport in Frog Corneal Epithelium by Decreasing K Permeability. Aldo Zamudio and Oscar A. Candia. Mount Sinai School of Medicine, New York, NY.

The cellular mechanisms involved in the effects of antidepressants such as fluoxetine (F) (which inhibits serotonin uptake at the synaptic cleft) and nortriptyline (N) remain poorly understood. Unrelated to this, we found that the histamine receptor (H_1) blocker diphenhydramine (D), inhibits, at 10^{-5} M, Cl transport across the isolated frog corneal epithelium. Because tricyclic antidepressants and fluoxetine bind to an intracellular histamine receptor (H_{1C}) (Brandes LJ, et al. Cancer Research 1992; 52:3796–3800.), we tested the effects of fluoxetine and nortriptyline (at 10^{-5} M) on Cl transport. Corneas were mounted in an Ussing-type chamber and bathed with Ringer's. The antidepressants reduced the Cl-originated I_{SC} by 50% while increasing the resistance by 30%. The effects were only observed from the apical side and could not be blocked by α-adrenergic antagonists. Microelectrode impalements showed a 20 mV cellular depolarization, consistent with a decreased basolateral K permeability. Corneas were also bathed with a high-K, Cl-free, Na-free solution on the apical side which was permeabilized with amphotericin B. Under this condition I_{SC} represents a K current across the basolateral membrane. This current was reduced by D (66%), F (46%) and N (55%). It seems that these drugs exert their cellular effects by interacting with apically-accessible H_1 or H_{1C} receptors which are linked to the regulation of K channels.

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Choroidal Vascular Tone-Potential Biochemical-Pharmacological Mechanisms. K. G. Schmidt, O. Geyer, and T. W. Mittag*. Departments of Ophthalmology & Pharmacology*, Mount Sinai School of Medicine, New York, NY.

The choroid, a low resistance vascular structure carrying 85% of the ocular blood flow, has important functions including providing nourishment to and removal of potential toxic waste products from the adjacent non-vascularized retina and optic disc region. Few studies exist examining the biochemical or pharmacological mechanisms for maintenance of choroidal vascular tone. Therefore, we have studied some basic characteristics of the adenylyl (AC) and guanylyl cyclase (GC) systems in the bovine choroid. Compared to respective baseline measurements (= 100 ± SEM%), AC responses were increased ($p < 0.05$) by forskolin (FSK, 477 ± 59%), fluoroaluminate (AIF_4, 360 ± 10.3%), isoproterenol (ISO, 129 ± 5.5%), vasoactive-intestinal peptide (VIP, 132 ± 6.1%), calmodulin (CAM) + Mn^{2+} (196 ± 69%), and dose-dependently by PGE_2 (up to 162 ± 3.6%). The antagonist drug Calmidazolium inhibited the CAM dependent increase but also blocked basal activity by 47 ± 2.0% at 50 μM without affecting the FSK response. Other CAM blockers (TFP, W5) produced similar results, but were not completely selective for CAM-cyclase. GDP β S did not affect AC responses to FSK, ISO, and ALF_4, but decreased the response to PGE_2. The adenosine agonist NECA did not influence FSK or ISO responses, and did not activate AC by itself. In the GC system activity was increased ($p < 0.05$) by CAM + Mn^{2+} (239 ± 27%), by atrial natriuretic peptide (up to 143 ± 1.4%) and sodium nitroprusside (up to 179 ± 1.6% at 10 μM).

Conclusions. These results show that choroidal tissue has significant activities of the adenylyl cyclase and guanylyl cyclase second messenger systems that may control the degree of relaxation in this vascular tissue.

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Control and Regulation of Cl Secretion by the Frog Corneal Epithelium. Oscar A. Candia and Aldo Zamudio. Mount Sinai School of Medicine, New York, NY.

Cl secretion is controlled by at least five elements of the transporting epithelial cell layer: the Na-K pump, Na-Cl (K) cotransporter, basolateral K and Na permeabilities and apical Cl permeability. To further elucidate the stoichiometry and relationship between the rates of Cl, Na and K transport the following experiments were made. Isolated frog corneas were placed in an Ussing-type chamber and bathed with a cell-like solution on the apical side and normal Ringer's on the basolateral side. I_{SC}, ^{36}Cl fluxes and ^{86}Rb fluxes (as a K label) were measured simultaneously in either direction (S = stroma; T = tear) under control conditions and after sequential treatment with amphotericin B (to permeabilize the apical membrane to ions), quinidine, ouabain and bumetanide. $J_{Cl,ST}$ was reduced by quinidine (due to cell depolarization), ouabain and bumetanide. $J_{Cl,TS}$ was reduced only by bumetanide. $J_{Rb,ST}$ was reduced by quinidine (45%), ouabain (36%) and bumetanide (19%). $J_{Rb,TS}$ was reduced by quinidine and bumetanide. The inhibition by the diuretic of $J_{Cl,ST}$ was twice its effect on $J_{Rb,ST}$. It is concluded that: (a) Cl movement across the basolateral membrane is bidirectional, limited to the cotransporter, and coupled to Na and K; (b) apical [Cl] in the range 0–100 mM has no influence on the rate of Cl secretion which is mainly controlled by the elements on the basolateral membrane and regulated by apical Cl permeability.

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Corneal Topography in Keratoconus Contact Lens Fitting. A. N. Cohen, M. J. Dunn, A. Bartolomei, and P. A. Asbell. Mount Sinai Medical Center, New York, NY.

Purpose. Traditionally contact lens fitting utilizes central keratometry readings to estimate the base curve for initial trial lens fitting. Best fit is eventually achieved through subsequent trial and error. This becomes even more important in keratoconus patients where there is a significant amount of asymetrical astigmatism. *Methods.* We examined 20 eyes of 12 patients with keratoconus which were successfully fitted with standard rigid gas permeable contact lenses to determine if there was a statistically significant correlation between the base curve (B.C.) selected and the keratometry readings obtained by corneal topography. *Results.* The average B.C. was 46.8 ± 6.1D. The average keratometry readings were at 3mm flat 47.0 ± 7.0D and steep 50.7 ± 9.0D; 5mm flat 45.35 ± 5.93D and steep 49.29 ± 7.82D; at 7mm flat 45.75 ± 4.76D and steep 48.18 ± 7.2D. There was no statistically significant correlation between the base curve and standard keratometry readings. Looking at the corneal topography we found that the area that best correlated with the B.C. was the transition zone where the topography changed from the steep area of the cone to the area of the flatter, more normal cornea. Keratometry readings at the 3, 5, or 7 mm diameter were not good predictors of the base curve used for best fit. *Conclusion.* No statistically significant correlation was found between the base curve selected and the keratometry readings. Corneal topography demonstrated a transition zone which was a good indicator for selecting the base curve. A computerized program is now being developed to automatically pick a base curve and simulate fluorescein patterns on the computer.

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The Effect of Brimonidine Tartrate in Glaucoma Patients on Maximal Medical Therapy. J. B. Serle(1), S. M. Podos(1), G. P. Abundo(2), R. Ritch(2), A. L. Coleman(3), W. C. Panek(3), C. E. Mantras(4). Mount Sinai Medical Center(1), and New York Eye & Ear Infirmary(2), New York, NY, Jules Stein Eye Institute(3), Los Angeles, CA, Allergan, Inc.(4), Irvine, CA.

Purpose. We evaluated the efficacy of the topical alpha$_2$-agonist, brimonidine tartrate, in delaying surgery in patients in whom present maximally tolerated glaucoma therapy was insufficient. *Methods.* In an open-labeled, non-comparative study, patients were treated with brimonidine 0.2%, b.i.d., in one or both eyes, in addition to existing maximally tolerated glaucoma medications. Study medication was titrated up to 0.5% brimonidine if necessary. Follow-up examinations were scheduled at one day, one week, 1, 2, and 3 months, and every three months for up to one year. *Results.* Of the 50 patients (74 eyes) enrolled, 47% (35 eyes) are still continuing therapy with 0.2% brimonidine. Twenty-two patients have undergone therapy with 0.2% brimonidine for at least three months. Mean follow-up time for all patients with 0.2% brimonidine was 106 days (min = 1, max = 327). The medication was titrated to the 0.5% concentration in 17 eyes (24%). The probability of successful treatment with 0.2% brimonidine for three months is 70%, and is 50% for more than six months. *Conclusions.* Brimonidine tartrate, used as adjunctive therapy, was effective in delaying surgery in patients on maximally tolerated medications.

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The Effect of Flurbiprofen (FL) on the Histopathology of Pigmented Rabbit Eyes after Contact Transscleral Nd:YAG Laser Cyclophotocoagulation (CYC). A. H. Friedman, K. G. Schmidt, C. B. Camras, and S. M. Podos. Ophthalmology, Mount Sinai School of Medicine, New York, NY.

The correlation of histopathologic changes after CYC with reduction of intraocular pressure (IOP) is unclear. Destruction of the secretory ciliary epithelium or liberation of prostaglandins may account for CYC's action. CYC (30 applications 360°, each at 3 W and 0.5 sec and centered 1.5 mm from the limbus) was performed in one eye each of 14 pigmented rabbits, and a sham procedure in the contralateral eye. In an additional 15 pigmented rabbits, both eyes underwent CYC, one eye treated with FL and the other with vehicle. The drops were applied every 30 min for 2 hrs before CYC, every 2 hrs for 24 hrs, and continuing every 6 hrs thereafter. IOPs were measured and eyes were histologically examined on day 1 and 17 following CYC. On day 1, in the group not receiving FL, the CYC-treated eyes ($n = 8$) showed coagulation necrosis of the inner sclera with vaporization of ciliary processes. IOP was reduced ($p < 0.0001$) by 12.0 ± 0.7 mmHg (mean ± SEM; $n = 14$) compared to baseline values. On day 17, these eyes ($n = 6$) showed atrophic areas in the inner sclera with overlying fibrous plaques and their IOP had returned to baseline values. On day 1, the eyes treated with CYC and FL ($n = 9$) displayed coagulation necrosis of the inner sclera. The overlying ciliary body was vaporized. IOP was reduced ($p < 0.0001$) by 12.8 ± 0.6 mmHg ($n = 15$) compared to baseline. On day 17, these eyes ($n = 6$) displayed a normal outer sclera. Fibrous plaques were present at the sites of ciliary body vaporization. IOP had returned to baseline values. There were no qualitative histopathological or IOP differences in eyes treated with FL or not.

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Effect of Oxymetazoline on Aqueous Humor Dynamics and Ocular Blood Flow in Monkeys and Rabbits. S. M. Podos, R-F Wang, P-Y Lee, T. Taniguchi, B. Becker*, J. B. Serle, I. W. Mattag. Departments of Ophthalmology, Mount Sinai School of Medicine, New York, NY and Washington University School of Medicine,* St. Louis, MO.

An investigation was carried out to determine the mechanism by which oxymetazoline, an α_2-adrenergic agonist, reduces intraocular pressure (IOP) when topically applied. Tonographic outflow facility (C), fluorophotometric aqueous humor flow (F), uveoscleral outflow (Fu) determined by a perfusion technique with FITC-dextran, and ocular peak pulse volume (PPV) determined by the Langham Ocular Blood Flow System were measured before and after therapy in the eyes of cynomolgus monkeys and albino rabbits. In 8 normal monkeys, C was unchanged ($p > 0.10$) at 2 hrs after single dose administration of 0.5% oxymetazoline, and F was significantly ($p < 0.001$) reduced by 37% over 4 hrs following 1% oxymetazoline [1.02 ± 0.05 μl/min (SEM) (treated) vs 1.62 ± 0.19 μl/min (contralateral)]. In 8 rabbits, Fu was significantly ($p < 0.005$) increased by 56% at 3 hrs after 0.1% oxymetazoline application [0.28 ± 0.02 μl/min (treated) vs 0.18 ± 0.03 μl/min (contralateral)]. 0.5% oxymetazoline did not alter PPV in the eyes of 6 normal and 5 glaucomatous monkeys.

The results suggest that oxymetazoline reduces IOP by decreasing aqueous humor flow and by increasing uveoscleral outflow.

The Effect of Prozac on Potassium and Sodium (Na) Currents in Lens and Corneal Epithelia. J. L. Rae,* A. J. Rich, and O. A. Candia†. Depts of Physiology and Biophysics and Ophthalmology, Mayo Foundation, Rochester, MN* and Depts. of Ophthalmology and Physiology, Mount Sinai School of Medicine†, New York, NY.

Prozac is a drug with antidepressive action in humans in doses of 0.3–1 μM. It also has blocking effects on at least 3 ion channels in lens and corneal epithelium when used at higher concentrations ($1.0–10.0 \times 10^{-5}$ M). In rabbit corneal epithelium, Prozac reduces the highly studied whole cell potassium current and causes cell depolarization when it is added to either a NaCl of KCl ringer bathing the cells. The current reduction is substantial at all voltages between −70 to +100 mV but not complete at positive voltages even when used at 1×10^{-4} M.

In cultured human and bovine lens epithelium, Prozac substantially reduces delayed rectifier potassium currents while having little effect on inward rectifying and calcium activated potassium currents. Again, 1×10^{-4} M Prozac is insufficient to totally block delayed rectification at positive voltages. Cultured human lens epithelium also expresses tetrodotoxin blockable sodium channels. These are also blocked substantially by Prozac in concentrations as low as 1×10^{-5} M, a block which is only partially reversible.

While the effective concentrations of Prozac required to block ocular potassium channels are higher than the therapeutic doses used in humans, they are as low or lower than those of other commonly used potassium channel blockers. Prozac may therefore prove to be a useful tool for dissecting different potassium conductances in ocular epithelia and elsewhere.

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The Effects of Isoproterenol and Forskolin on the Phagocytosis of Rod Outer Segments by Retinal Pigment Epithelial Cells Are Independent of cAMP and Protein Kinase A.

Shoji Kuriyama(1), Michael O. Hall(1), Toshka A. Abrams(1), and Thomas W. Mittag(2). Jules Stein Eye Institute, UCLA School of Medicine, Los Angeles, CA(1), and Department of Ophthalmology, The Mount Sinai Medical Center, New York, NY (2).

Purpose. We have studied the involvement of cAMP dependent second messenger systems in the inhibition of ROS phagocytosis by isoproterenol (ISO) and forskolin (FSK) using two membrane permeant analogs of cAMP, the Rp and Sp diastereomers of cyclic adenosine 3′,5′ monophosphothioate (cAMPS), and antisense oligodeoxynucleotides to Gs protein α-subunit sequence (Gsα). *Methods and Results.* Rp-cAMPS is a particularly potent competitive inhibitor of PKA, whereas Sp-cAMPS is a potent activator of this enzyme. Sp-cAMPS showed a dose-dependent inhibition of ROS phagocytosis ($ID_{50} = 10\ \mu M$), while Rp-cAMPS had no effect on this process. Rp-cAMPS prevented the inhibitory effect of Sp-cAMPS, but had no effect on the inhibition of ROS phagocytosis induced by ISO and FSK. ISO plus FSK showed an additive effect on phagocytosis, while ISO plus Sp-cAMPS and FSK plus Sp-cAMPS did not. RPE cells were treated with antisense Gsα oligodeoxynucleotides, after which the ability of ISO to inhibit phagocytosis was measured. The treated cells showed a greatly decreased inhibition of phagocytosis (30% of control, untreated cells). This indicates that Gs is directly associated with the inhibitory effect of ISO. *Conclusion.* Our results suggest that ISO and FSK inhibit ROS phagocytosis by RPE cells through a cAMP-independent (PKA-independent) pathway, as well as through a cAMP-dependent one. The cAMP-independent pathway may be mediated directly through a G protein.

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Effects of Medetomidine (MED) on Intraocular Pressure (IOP), Pupil Diameter and Uveoscleral Outflow in Rabbits.

P-Y Lee, J. B. Serle, and S. M. Podos. Department of Ophthalmology, Mount Sinai School of Medicine, New York, NY.

Recent studies have demonstrated that MED, a selective alpha-2 agonist, with affinity for alpha-2 receptors that is approximately three times higher than clonidine, decreases IOP in rabbits. The mechanisms which cause this IOP reduction are not known. To explore possible mechanisms, IOP was measured by pneumatonometry, and uveoscleral outflow (Fu) was determined by a perfusion technique with FITC-dextran. Pupil diameter (PD) was measured with a clear millimeter ruler in normal room light. IOP and PD measurements were taken at 0 hr, 0.5 hr, and hourly for a total of 6 hrs on one baseline day with vehicle administration, and subsequently after 25 µl of 0.1%, 0.5% or 1% MED was applied to one eye and an equal volume of vehicle to the contralateral eye in 6 rabbits. IOP was significantly ($p < 0.05$) reduced bilaterally and PD was significantly ($p < 0.01$) increased in the treated eyes after 0.1% MED. The 0.5% and 1% concentrations of MED resulted in ($p < 0.02$) IOP and PD effects of greater magnitude than 0.1%. Fu was measured 2 hrs after 25 µl of 0.5% MED was applied to one eye of 8 rabbits. MED produced a significant ($p < 0.005$) increase in Fu in the treated eyes (0.40 ± 0.04 µl/min) and contralateral control eyes (0.36 ± 0.04 µl/min) compared to 13 untreated eyes (0.23 ± 0.01 µl/min).

Our results indicate that in rabbits MED reduces IOP bilaterally following unilateral topical application. This IOP reduction is due in part to an increase in Fu.

Effects of Topical Ethacrynic Acid (EY-105) Ointment on Intraocular Pressure (IOP) in Glaucomatous Monkeys.

R-F. Wang, J. B. Serle, S. M. Podos, A. H. Neufeld*, R. Deschenes*. Department of Ophthalmology, Mount Sinai School of Medicine, New York, NY, and Telor Ophthalmic Pharmaceuticals, Inc.*, Woburn, MA.

Ethacrynic acid, a sulfhydryl reactive drug, reduces IOP and increases outflow facility in normal monkeys. In the present study, the effect of topical EY-105 ointment on IOP was evaluated in 4 monkeys in which glaucoma was induced by argon laser treatment of the trabecular meshwork. IOP was measured daily at 0 hr, 0.5 hr and hourly for 7 hrs during one baseline day, one vehicle-treated day, and five days of therapy with 0.5%, 1.0%, 1.5% or 2.5% EY-105 ointment applied once daily at 9:00 a.m.

IOP was not different comparing baseline and vehicle-treated days. All four concentrations of EY-105 ointment reduced IOP, although the onset of IOP reduction did not occur until after the second dose with any of the concentrations. The magnitude of the IOP reduction was dose-dependent. The mean maximum reduction in IOP was 8.5 ± 2.9 mmHg (SEM). A more pronounced reduction in IOP was observed on the 5th day of treatment for each of the 4 concentrations. An effect on IOP was observed for 24 hours after a single dose. Mild conjunctival hyperemia and discharge appeared in some eyes treated with the three highest concentrations. The corneas remained clear. Neither aqueous flare nor anterior chamber cellular response were apparent. EY-105 ointment may prove to be useful in glaucoma therapy.

Indocyanine Green (ICG) Enhancement of Diode Laser Cyclophotocoagulation in Rabbits.

Steven A. Odrich, Gregory L. Cowan, Francis J. Wapner, Alan H. Friedman, Steven M. Podos. Mount Sinai School of Medicine, New York, NY.

Purpose and Methods. In order to assess the effect of intravenous ICG on diode laser contact cyclophotocoagulation (CPC), six pigmented rabbits received diode CPC under sedation and topical proparacine. Each animal's right eye received no pre-treatment. Immediately before treatment of their left eyes, animals were administered 1.0 ml of intravenous ICG (5 mg/ml). CPC was then performed in an identical manner as in the contralateral eye. Each treatment, applied 1.0 mm posterior to the limbus, consisted of a single 1.0 second pulse. At every second treatment site output energy was increased by 0.1 J, starting with a sub-threshold 0.1 J/pulse and peaking at the supra-threshold level of 1.0 J/pulse. Threshold energies were defined as 0.6–0.7 J for diode CPC in rabbits. Three animals were sacrificed at 24 hours, and three at 72 hours using barbiturate overdose. All eyes were enucleated and prepared for sectioning and staining. *Results.* Gross examination revealed that two ICG-treated eyes had spontaneously ruptured at the sites of laser application using threshold energy levels. No such findings were seen at any energy level in eyes not pre-treated with ICG. On histologic examination it was found that CPC lesions in the eye of an animal pre-treated with ICG demonstrated more extensive coagulative necrosis than did lesions created with equal energies in the same animal's control eye. *Conclusions.* Intravenous ICG appears to decrease the threshold energy at which ablation of ocular tissues is achieved using the diode laser, while increasing the risk of significant complications including destructive coagulative necrosis of non-targeted ocular tissues, weakening of the eye wall, and frank rupturing of the globe. Appropriate and safe energy levels must be established before this technique is attempted in humans.

This postdoctoral fellowship has been awarded in honor of Elsie K. Sloate by the Fight for Sight Research Division of the National Society to Prevent Blindness.

Evaluation of Chemotaxis by Various Cytokines of Ia$^+$ Langerhans Cells into the Central Cornea of Mice. S. P. Epstein[1], M. S. Jan, and P. A. Asbell[1]. Department of Ophthalmology, Mount Sinai Medical Center, New York, NY.

Purpose. Under normal conditions the central cornea is devoid of Ia$^+$ Langerhans cells (LC). We sought to determine which cytokines are chemotactic for LC in the cornea. *Methods.* 50 BALB/c and 50 C57BL/6 mice were injected with a single intracorneal injection of 200 U recombinant (r) murine (m) IL-1α, 0.004 U r mu IL-1β, 250 U r mu IL-2, 1000 U r mu IL-6, 10 U natural (n) human TNF-α or 25 U n mu GM-CSF. After a 2 hour (h) incubation, they were indirectly immunoperoxidase stained with rat anti-mu Ia antibody. *Results.* Unstimulated corneas were found to contain 0 to 3 Ia$^+$ LC. IL-1β, IL-6 or TNF-α induced the migration of 8.3 ± 2 BALB/c and 11.8 ± 4 C57BL/6 Ia$^+$ LC/cornea; while IL-2 induced the migration of 25.5 ± 9 Ia$^+$ LC in BALB/c, but only 12.2 ± 4 Ia$^+$ LC in C57BL/6 mouse corneas. Intracorneal injection of IL-1α, or GM-CSF were not chemotactic for LC and incubations as long as overnight (~16 h) failed to elicit any greater chemotaxis than those of 2 h for any of the cytokines studied. To determine whether the effect of each cytokine was directly on LC or via the induction of a common intermediary, we investigated whether Cyclosporine A (CsA) could abrogate the cytokine-mediated chemotaxis of LC into the cornea. In the presence of 5 μg CsA, both IL-2 and TNF-α remained chemotactic for LC, while the chemotactic effects of IL-1β and IL-6 were completely abrogated. *Conclusions.* We propose that IL-2 and TNF-α are directly chemotactic for LC, whereas IL-1β and IL-6 act through the induction of either IL-2, TNF-α or both.

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Evidence for a Bumetanide-Sensitive Na-K-CI Cotransporter in Cultured Bovine Lens Epithelial Cells. Lawrence J. Alvarez, Aldo Zamudio, J. Mario Wolosin, and Oscar A. Candia. Mount Sinai School of Medicine, New York, NY.

Previous studies on the cells noted above indicated indirectly that a Cl-uptake mechanism was present (ICER, 1992). This notion arose to explain the finding that the Na-H exchanger was only activated by hypertonicity if the cells were either pre-exposed to bumetanide or pre-equilibrated under Cl-free conditions. Using ^{86}Rb as a label for K recent experiments have demonstrated directly the presence of the inferred transport activity. Epithelial monolayers (10 cm^2) were incubated in a HEPES-buffered physiological solution in the presence of the label for 10 min. The counts were extracted in TCA and measured in a gamma detector; protein was digested in NaOH for measurement by the Lowry assay. An influx rate of 1.51 ± 0.43 μEq/mg · hr (±SD; $n = 13$) was calculated. The bumetanide-sensitive component represented 43 ± 7% ($n = 6$) of the influx. The combination of bumetamide plus ouabain inhibited 98 ± 2% ($n = 6$) of the uptake. In Cl-free solutions, bumetanide did not affect the baseline uptake (1.03 ± 0.27; $n = 6$), which was inhibited by 97 ± 3% upon ouabain addition ($n = 4$). The small influx in the presence of the 2 inhibitors indicated little passive movement of label via K channels, suggesting a relatively depolarized cell system. Preliminary microelectrode impalements provided values of about −25 mV, a level consistent with the literature for the intact bovine lens. It is suggested that the humetanide-sensitive pathway also exists in the lens.

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Focal ERG Phase-Lag in Diabetic Macular Edema. S. E. Brodie,(1,2) D. E. Sperber,(2) and M. Hope-Ross.(2) Mount Sinai School of Medicine,(1) Manhattan Eye, Ear & Throat Hospital,(2) New York, NY.

Purpose. We recorded focal electroretinograms (FERG) from patients with diabetic macular edema in an attempt to confirm previous reports of substantial phase lags with normal FERG amplitude in such patients. *Methods.* FERG recordings were obtained using the Doran Instruments Maculoscope stimulator ophthalmoscope, which images a five-degree flickering central spot on the macula under ophthalmoscopic control, surrounded by a brighter steady annulus to desensitize the more peripheral retina to scattered light. Patients were selected from the retina clinic at Manhattan Eye, Ear & Throat Hospital. Macular edema was confirmed by fluorescein angiography. Patients who had undergone prior focal laser treatment were excluded. Informed consent was obtained from all participants. *Results.* FERG recordings in our patients demonstrated phase lags of 120 degrees or greater, compared with an upper limit of normal of 95 to 100 degrees. *Conclusions.* The pronounced phase-lag of the FERG seen in diabetic macular edema appears to be a more robust abnormality than the small reductions in Ganzfeld ERG amplitude previously reported in this patient population.

Supported by grants from Research to Prevent Blindness, the LuEsther Mertz Retina Research Fund, and the Manhattan Eye, Ear & Throat Hospital Foundation.

Identification of a Novel WGA-Binding Integral Membrane Protein Associated with Corneal Epithelial Cell Stratification. Gabriel J. G. Hou and J. Mario Wolosin. Mount Sinai School of Medicine, New York, NY.

Previous studies have shown that all intrastratal suprabasal (SB) cells of the rabbit corneal epithelium, when exposed to the outer corneal surface by the digitonin-induced exfoliation of overlying cell layers, display high levels of WGA and Con A binding sites at their apical membranes, whereas the apically-facing membranes of the basal (B) cells lack these sites (IOVS *31*, 294). To determine whether this difference could reflect differences in glycoprotein complements between the SB and B cells, the following protocol was carried out. Corneas were incubated in Jocklick's modified MEM with 5 μM Ca^{+2} for 20 hours, eliciting the release of all SB cells from the corneal surfaces. These cells and the basal monolayer were then collected and processed in parallel for Western blot analyses using agglutinins derived from wheat germ (WGA), *Sambucus nigra* (SNA), *Maakia amurensis* (MAA) and peanut lectin agglutinin (PNA). Lectins were selected because of their intense and sialic acid-inhibitable binding to the corneal surfaces. SNA and PNA showed no substantial SB/B differences. MAA showed only quantitative increases with stratification. WGA uniquely identified a 94 Kd band present solely in SB cells not recognized by the other three lectins. This protein was recovered in the particulate fraction of a cell homogenate from which was completely solubilized by Triton X-100. Removal of sialic acid by sialidase abolished the ability of WGA binding yet recovered the PNA binding. These results indicated the existence of a novel stratification-associated membrane glycoprotein.

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Interferon-Induced Chemotaxis of Ia$^+$ Langerhans Cells into the Cornea. A. Asbell(1), M. S. Jan, and S. P. Epstein (1). Dept. of Ophthalmology(1), Mount Sinai Hospital, New York, NY.

Purpose. Ocular herpes simplex (HSV) infection induces the migration of Langerhans cells (LC) into the cornea. HSV keratitis is known to stimulate interferon (IFN) production within the cornea. IFN's have been proposed for treating HSV keratitis. The IFN's were evaluated for chemotactic activity upon LC. *Methods.* Mouse corneas were injected with 2000U IFN-α or 500U IFN-γ, each with and without 0.004U Interleukin (IL)-1β, 250U IL-2 5μg Cyclosporine A (CsA) and then indirectly stained for Ia antigen after a 2 h incubation. *Results.* IFN-α produced a migration of 11.8 ± 3.1 LC/cornea into the BALB/c corneas and 8.0 ± 1 LC/cornea into the C57BL/6 corneas. In the presence of 5μg CsA, IFN-α failed to elicit any significant levels of chemotaxis in either strain (BALB/c: 1.0 ± 1; C57BL/6: 1.0 ± 1 LC/cornea). IFN-γ elicited the migration of only 0.86 ± 1 LC/cornea in the BALB/c and 0.50 ± 0.84 in the C57BL/6 strain. Since IFN-γ has been reported as having some inhibitory properties, IL-1β or IL-2 was injected into the same corneas which had been injected with IFN-γ. Both those corneas injected with IFN-γ followed by IL-1β, as well as those injected with IFN-γ followed by IL-2, induced the migration of ≈27.7 ± 4 and 27.8 ± 1 (IL-1β: 27.8 ± 1; IL-2: 27.9 ± 2) LC/cornea in the C57BL/6 mice. *Conclusions.* These results suggest that the IFN's may have a role in LC migration into the cornea in diseases such as herpetic keratitis; IFN-α by itself, while IFN-γ in conjunction with other cytokines which may be produced as a result of the ocular infection.

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Low-Cost 24-Bit Color Contrast Screening for Early Glaucoma. R. M. Fischer(1), J. Hirsch(2), and S. E. Brodie(1). Mount Sinai School of Medicine(1), and Memorial-Sloan Kettering Cancer Center(2), New York, NY.

Purpose. Recent reductions in the price of 24-bit "True Color" graphics adapters for PC-compatible computers have enabled low-cost emulation of the midperipheral color-contrast targets recently described for the early detection of glaucoma by Arden et al [Clin Vision Sci. 2:303–320, 1988; IOVS 32:2779–2789, 1991]. We have developed such a system, which can be installed on a Windows-capable PC with VGA graphics for an incremental cost of $200. A working version of the system will be demonstrated. *Methods.* Tritan-axis stimuli were implemented as large "Landolt C's" against desaturated red and green backgrounds, matched to chips 85 and 42 from the Farnsworth-Munsell 100-Hue test. Tritan-axis contrast was effected by small variations in the intensity of the blue component of the stimulus color. For low-contrast tritan-axis targets near threshold, we found no necessity to correct these stimuli for luminance variation, due to the minimal contribution to the photopic luminance of the blue stimulus component, as measured with a calibrated photometer. *Results.* Trials in patients with confirmed glaucoma indicate mid-peripheral tritan contrast thresholds two to three times those in normal controls. Some glaucoma suspects show lesser degrees of reduction in tritan contrast sensitivity. *Conclusions.* 24-bit graphics using the standard VGA monitor is potentially valuable as a low-cost screening tool, within the reach of the clinical practitioner.

Supported by a grant from Research to Prevent Blindness.

Mediation of Corneal Inflammation through the use of TGF-Beta. A. Bartolomei, P. A. Asbell, S. P. Epstein. Dept. of Ophthalmology, Mount Sinai Medical Center, New York, NY.

Purpose. The migration of Langerhans cells (LC) has long been suspected as being important in antigen presentation in surface tissues. Transforming Growth Factor (TGF)-β is a cytokine, which has a variety of both inhibitory and immunosuppressive properties. Since corneal epithelium is normally devoid of Ia$^+$ LC, we investigated whether the effect of TGF-β on LC chemotaxis in the cornea is similar to that of Cyclosporine A (CsA). *Methods.* 0.004U recombinant (r) murine (mu) Interleukin (IL)-1β, 250U r mu IL-2, 1000U r mu IL-6, or 10U ultrapure natural human Tumor Necrosis Factor (TNF)-α were intracorneally injected into the corneas of BALB/c and C57BL/6 mice both with and without 41.5ng natural TGF-β. Following a 2 hour incubation, the corneas were stained for LC utilizing a rat anti-mu Ia antibody in an indirect immunoperoxidase technique. *Results.* As previously reported, the cytokines, without TGF-β, all induce the migration of Ia$^+$ LC into the corneas of BALB/c and C57BL/6 mice. IL-1β, in the presence of TGF-β, failed to be chemotactic (BALB/c: 0.25 ± 0.6; C57BL/6: 0.33 ± 0.7), while IL-2, TNF-α *and* IL-6 in BALB/a mice all not only remained chemotactic for LC (28.0 ± 4.9 Ia$^+$ LC/cornea), but were elevated to levels of chemotaxis previously only attainable by IL-2 (25.5 ± 9 Ia$^+$ LC/cornea: $p \geqslant 0.26$). TGF-β with IL-6 in C57BL/6 mice (0.58 ± 0.7 Ia$^+$ LC/cornea) abrogated the chemotactic effect of IL-6 alone (12.2 ± 4 Ia$^+$ LC/cornea: $p \leqslant 0.0001$). *Conclusions.* Findings suggest that, at least in BALB/c mice, TGF-β may upregulate LC chemotaxis via the inhibition of biofeedback mechanisms.

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Nitric Oxide Synthase: Distribution and Biochemical Properties of the Enzyme in the Bovine Eye. O. Geyer*, S. M. Podos*, T. W. Mittag*,†. Depts. of Ophthalmology* and Pharmacology†, Mount Sinai School of Medicine, New York, NY.

Nitric oxide (NO) is a short-lived free radical that mediates vascular relaxation via endothelial cells, cytotoxic actions of macrophages and neutrophils, and may be a transmitted substance in neural tissue. Immunohistochemical identification of NO synthase (NOS) showed a strong presence in the retina and choroid (Yamamato et al, IOVS 33, Abstr #3604, ARVO 1992). We have investigated NOS levels and basic biochemical characteristics in various ocular tissues of the bovine eye by measuring ^{3}[H]citrulline formation that accompanies the formation of NO from arginine. Retinal NOS was >75% associated with the cytosolic fraction, required O_2, L-arginine and NADPH, and was inhibited by N^Gnitro-L-arginine. The soluble enzyme required both free Ca^{2+} and Mg^{2+}, and was inactive when either cation was absent. However retinal NOS activity was supported by 1–10 μM Mn^{2+} ions alone. Compared to control baseline activity (with 4 mM Mg^{2+}, 250 μM Ca^{2+}, 450 μM EDTA present) = 100 ± SEM%, retinal NOS activity was increased by addition of 1 μm tetrahydrobiopterin (+82 ± 9.2%), was unchanged by the addition of FAD (4 μM) + FMN (4 μM), but was increased up to 300% when all three cofactors were present. Thus, electron transfer cofactors may be rate-limiting and availability of biopterin may be a physiological regulator of NOS. Cytoplasmic fractions of other tissues in the eye also showed NOS activity. Relative to the retinal activity (2–4 p mol/min/mg protein at optimal substrate, divalent cation and cofactor conditions) = 100%, the NOS specific activity was approx. equal in choroid and retina, was 23 ± 1–4% in ciliary processes and 34 ± 17.7% in trabecular meshwork. *Conclusions.* These results show that nitric oxide synthase is widely distributed in various ocular tissues. NOS enzymes in the eye may have unique biochemical properties and specific physiological functions in several intraocular tissues.

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Physiological Evidence for a Membrane-Bound Carbonic Anhydrase in the Corneal Epithelium. Xiao-Ping Shi, Oscar A. Candia, Aldo Zamudio, and Per Wistrand*. Mount Sinai School of Medicine, New York, NY, and Uppsala University, Uppsala, Sweden*.

Based on the inhibition of transepithelial $H^{14}CO_3/^{14}CO_2$ fluxes by carbonic anhydrase (CA) inhibitors, we predicted that the enzyme must be present in the corneal epithelium (ARVO 1991). This has now been confirmed by microchemical detection (Exp. Eye Res., 55:637, 1992). We also found that under 5% CO_2 the unidirectional tear (T) to stroma (S) flux $J_{14C,TS}$ was larger than $J_{14C,ST}$ (3.56 vs 2.65 μEq/hr · cm^2). This net flux was CO_2 but not HCO_3 dependent. There are no reasonable models by which the cytoplasmic CA can provide directionality to the CO_2 movement. However, this unusual CA-dependent CO_2 flux could be understood if the asymmetry was provided by a membrane-bound enzyme. If CA resides at the basolateral membrane it could add in the conversion of HCO_3 to CO_2 due to the low pH environment just outside the basolateral membrane. We have tested the effects of two membrane-impermeable CA inhibitors, quaternized sulfanilamide (QS) and benzolamide, on $J_{14C,ST}$ and $J_{14C,TS}$ across the isolated frog cornea. QS (10^{-3} M) reduced $J_{14C,TS}$ from 2.95 ± 0.10 to 1.95 ± 0.04 and $J_{14C,ST}$ from 1.98 ± 0.09 to 1.68 ± 0.07 $\mu Eq/hr \cdot cm^2$ only when added to the stromal side. Benzolamide (10^{-4} M) had effects on $J_{14C,TS}$ and $J_{14C,ST}$ similar to QS. We also found that benzolamide inhibits I_{SC} across the isolated rabbit ciliary epithelium. Based on these results we propose that there is membrane-bound CA at the frog corneal epithelium and rabbit ciliary epithelium.

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Stratal Distribution and Synthesis Induction of a Tight Junction Protein in Rabbit Corneal Epithelium. Yu Wang and J. Mario Wolosin. Mount Sinai School of Medicine, New York, NY.

Tight junctions (TJs) are located between the squamous (SQ) superficial cells (SPC) of the corneal epithelium. We have previously shown through measurements of transepithelial resistance that a) digitonin-elicited devitalization of the SPC layer induces rapid, synthesis-independent assembly of TJs (1 hr) in the previous sub-SPC layer and b) when all three SQ layers are simultaneously devitalized, TJ formation by the exposed wing (W) cells start after a 2 hr delay, proceed through the next 10–15 hr and requires gene expression and protein synthesis (J Membr. B.104, 45; IOVS 32 (suppl), 1976), i.e., proteins critical for this assembly are synthesized as cells approach the surface in the course of stratal migration. We have now determined the stratal distribution of ZO-1, a TJ protein, and its changes during this induced synthesis-dependent TJ formation. Immunohistology showed: a) no detectable ZO-1 in basal (B) cells; b) scarce punctuate focal accumulations in the W cells; c) numerous foci in the SQ cells as well as diffuse cytosolic staining; and d) strong staining at the apical TJ locations in the SPC layers. Immunoblot analysis of separated layers showed a B:W:SQ [ZO-1] distribution of 0.02:0.16:1. Devitalization of the SQ layers induced strong ZO-1 synthesis. Its concentration in the remaining B and W component (20% of the original total) increased 3 to 5-fold after 8 and 20 hr, respectively. The synthesis concentrated in the outer W cells were electron microscopy showed time-dependent development of TJs. Similar responses were attained in the B cells after removal of all suprabasal cells by a low $[Ca^{2+}]$ incubation method. These results provide a biochemical correlate to our previous electrophysiological studies and demonstrate the value of cell exfoliation methods to study corneal epithelial cell maturation.

NIH EY 07773 and (CCG) EY 01867.

Structural Integrity of the Eye after Intrastromal Corneal Ring Insertion. L. G. Alcaraz, A. Bartolomei, C. P. Hurley, and P. A. Asbell. Department of Ophthalmology, Mount Sinai Hospital, New York, NY.

Purpose. Intrastromal corneal ring insertion is a procedure designed for the surgical correction of ammetropia. Since previous research in our laboratory has shown that radial keratotomy in cadaver eyes weakens the eyeglobe, we designed a study to evaluate the effect of the intrastromal corneal ring on the structural integrity of the eye. *Methods.* Twelve eye banks were dehydrated by immersion in dextran solution. Intrastromal corneal rings were inserted in 6 eyes by placing the plastic ring in a channel made at 2/3 peripheral corneal depth; an additional six eyes were held as controls without surgical manipulation. In both groups, intraocular pressure was increased by pumping normal saline through the optic nerve until leakage was noted or maximum pressure was reached. This was recorded as the burst pressure of that eye. *Results.* Mean burst pressure of the intrastromal corneal ring eyes (1267.8 ± 132) was statistically identical ($p = 0.94$) to the control eyes which had an average burst pressure of 1262 ± 95.6 mmHg. No leakage was detected at the wound site at any time before the eyes reached the maximum pressure obtainable. *Conclusions.* This study suggests that intrastromal ring insertion does not alter the structural integrity of the eye and does not weaken the cornea.

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Studies on DARP Expression in Bovine and Human Eyes Using PCR Based Techniques. J. Danias*, H. Kobayashi*, T. Mittaq*,†, S. M. Podos*. Departments of Ophthalmology* & Pharmacology†, Mount Sinai School of Medicine, New York, NY.

DARPP-32, a phosphoprotein found in CNS and kidney may regulate protein phosphatase and Na, K-ATPase. DARP-related proteins in bovine ciliary processes (CP), trabecular meshwork (TM), and aqueous humor (AH) occur in two distinct forms of ~38kDa and ~100kDa. Glycosylatin of the 32 kDa core protein gives rise to the 38 kDa form (Kobayashi, H. and Mittag, T., IOVS, 33: Abstract #2329, ARVO 1992).

Mouse Ltk cells transfected with DARP-32 cDNA (kindly provided by Dr. Christian Pifl, Cell Biology, Duke University) were studied to determine whether DARP-100 also arises by post-translational modification of a precursor. Western blotting of the Ltk cell proteins with DARP-specific antibodies stained a prominent band near 32kDa but not at 100kDa; evidence against DARP-100 arising from the smaller DARP-32 precursor, as is the case for the 38kDa form. The absence of transcripts larger than 1.8 kb in repeated Northern blots of CP mRNA using DARP-32 coding region probes suggested that DARP-32 and DARP-100 share some protein homologies but derive from different genes.

DARPP-32 made in CP and secreted into AH could have a signal role between CP and TM. We investigated this possibility by amplifying randomly primed cDNA from bovine CP and TM using DARP-32 specific primers. At equal levels of simultaneous amplification of the internal control protein cyclophyilin, the DARP-32 amplification product (213bp) was formed from CP cDNA in large excess compared to TM, indicating little capacity for TM to synthesize DARP-proteins. To confirm synthesis of DARP in CP but not TM in the human eye, we used the novel technique of in-situ PCR amplification of RNA message. DARP cDNA was amplified after in-situ reverse transcription on formalin fixed, paraffin blocked pathology tissue sections of the human eye. Sense primers were used as control for the PCR. Human CP epithelial cells were positive for DARP mRNA and thus may be a source of the DARP-32 present in human AH.

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Terminal Glycosylation in Rabbit Corneal Epithelium. Meiling Chen and J. Mario Wolosin. Mount Sinai School of Medicine, New York, NY.

Sugar-sequence specific FITC-lectins were applied to triton x-100-delipidated cryostat sections of rabbit corneas to analyze the development of protein terminal glycosylation in the epithelium as a function of stratal coordinates. *Sambuca nigra* agglutinin stained the plasma membrane (PM) of all the cells within the strata, indicating the presence of, galactose 2-6 sialyl transferase activity, from the basal (B) cell upwards. *Maakia amurensis* (MAA), a marker for galactose 2-3 sialyltransferase activity, stained faintly the PM of the B and first suprabasal (FSB) cell layers, and intensively, all layers above the FSB. Peanut lectin agglutinin (PNA), an indicator of galactose 1-3 galactosyltransferase (1-3 GT) activity stained exclusively intracellular locations in the FBS layer. The granular appearance of the stain and its base-to-apex distribution suggests Golgi localization. There was no substantial stain in either the PM or in the other cell layers. Blocking new glycosylation for 4 hr in organ culture with tunicamycin did not diminished or modified this staining pattern. Because PNA binding is known to be blocked by sialylation of the terminally exposed galactose these results indicate that the initial stratification event is critically associated with either a marked activation of a 1-3 GT and/or a decrease/intracellular relocation of STs allowing sustained accumulation and storage of nascent glycoproteins terminating on galactose residues within the FSB cell. The MAA binding pattern suggests that upon further upwards migration, increases in STs result in capping of the exposed terminal galactose residues and possibly, transport to the PM.

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Two Different Classes of Adenylyl Cyclase in Ciliary Processes.

W. B. Gud*, K. Kobayashi*, and T. W. Mittaq*,†. Departments of Ophthalmology*, and Pharmacology†, Mount Sinai School of Medicine, New York, NY.

Purpose. Adenylyl cyclase (AC) is thought to play a major role in the regulation of aqueous humor secretion by ciliary processes. Biochemical as well as genetic evidence suggests multiple types of membrane-associated adenylyl cyclase. We have previously demonstrated a bicarbonate stimulated AC activity in bovine ciliary processes. This membrane bound HCO_3-sensitive AC is not dependent on GTP and is additive with the Gs-mediated AC response to isoproterenol (lSO) in ciliary process particulate fractions (T. W. Mittag, et al., IOVS 33: ARVO abstract 1056, 1992). *Methods and Results.* The effects of 9-carboxyanthracene (9-CA) and fluorenecarboxylic acids (FC) were investigated on AC. At least two classes of AC were present in the bovine ciliary process; type a, activated by receptors coupled to Gs-proteins (e.g., ISO sensitive AC) and type b, activated by HCO_3. Both type a and type b AC interact with forskolin (FSK) because FSK potentiated AC responses to ISO and also to HCO_3. However 9-CA interacted differently with the two classes of AC. Addition of 9-CA increased basal and HCO_3 stimulated AC in a concentration-dependent manner (EC_{50} 0.85 mM) by up to +90% and by two-fold respectively. In contrast, addition of 9-CA inhibited the lSO and the FSK responses of AC noncompetitively (IC_{50} 5 mM and 10 mM respectively). 9-FC was similarly active but less so active than 9-CA, while other position isomers (1 and 4 FC) were inactive. *Conclusions.* These findings indicate that AC enzymes have a binding site for polyaromatic carboxylic acids of defined structure. This site can modulate catalytic activity causing inhibition of type a, Gs-activated AC, but potentiating the type B, Gs-independent AC.

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Variability of Optic Nerve Head Parameters Using the Heidelberg Retinal Tomograph.

G. Shafranov, R. A. Schumer, J. S. Lustgarten, and S. M. Podos. Department of Ophthalmology, Mount Sinai School of Medicine, New York, NY.

Purpose. We used the Heidelberg retinal tomograph (HRT) to image optic nerve heads (ONHs) of patients with and without glaucoma. We assessed variability of measurement of various extracted topographic parameters. *Methods.* HRT is a confocal laser tomographic imaging system yielding 32 parallel images each arising largely from the focal plane. A high-resolution topographic surface representation of the ONH was derived, and quantitative parameters of interest were extracted. The 32 images from an area centered on the ONH spanned a depth range of from 1 mm to 3.5 mm. We used 3 different areas of measurement: 10° × 10° (n = 13), 15° × 15° (n = 19), or 20° × 20° (n = 5). There were 9 patients with open-angle glaucoma (GL), 10 suspect for GL (GS), and 18 who were normal (NL). *Results.* Mean # images/eye was 4.7 (range: 3–6). Across all groups, coefficient of variation (standard deviation ÷ mean) (COV) was calculated for: excavation area (EA): 7.54%; maximum excavation depth: 9.96%; mean excavation depth: 9.98%; disc volume: 12.2%; excavation volume: 12.2%. For parameter EA, COV depended on area of measurement: 4.95% ($100^{\circ 2}$), 7.42% ($225^{\circ 2}$), or 9.97% ($400^{\circ 2}$) ($p < 0.05$). For other parameters, COV was independent of area of measurement. COVs for GL v. GS v. NL were not different. *Conclusions.* Variability of the HRT parameters appears acceptable and not to depend on ONH damage.

Book Reviews

Gastric Peptic Secretion

R. Cheli, A. Perasso, and G. Testino, editors. Verona: Cortina International, 1990. 128 pp, ill. $50.00. ISBN 88-7749-064-0.

THIS BOOK is a compilation of 14 short review papers which were originally presented at a course dedicated to this subject given at the Advanced School of Oncology and Biomedical Sciences at Santa Margherita Ligure, Italy. All the authors are based in Italian centers. This monograph provides a thorough and comprehensive review of most aspects of pepsin and the pepsinogens. The bibliography is critically selected and fairly complete; however, literature references are not more recent than 1988 with a few exceptions. The only glaring omission is in regard to the pepsinogen immunohistochemical studies of Tatematsu and his Nogoya group.

The clarity of language varies considerably from author to author and the language at times is difficult. Introductory paragraphs precede each short chapter, and these are sometimes repetitious in recounting historical references.

These shortcomings notwithstanding, the overall value of the book rates high as a reference source and provides good critical reviews in most areas of pepsin and pepsinogen physiology in health and disease. The papers (chapters) are brief and concise. The authors provide personal viewpoints along with some well-annotated reviews of the literature.

Particularly recommended for the reader's consideration are the chapters on normal morphology (Chapter 1); the regulation of pepsin secretion (Chapter 2); chief cell mass and pepsinogen I in chronic gastritis (Chapter 11); and the effect of antisecretory drugs (Chapter 14).

This monograph presumes a significant level of expertise on the part of the reader. Serious students of pepsinogen and pepsin physiology will not be disappointed.

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Non-Responders in Gastroenterology: Causes and Treatments

G. Dobrilla, K. D. Bardhan, and A. Steele, editors. Verona: Cortina International, 1991. 236 pp, ill. $174.00. ISBN 88-7749-065-9.

THE TITLE of this book, *Non-Responders in Gastroenterology,* immediately stimulated my interest, since we as physicians are all faced with patients who simply do not respond to medical treatment. Nonresponse may occur for many reasons, including the simplest, such as noncompliance, to the more difficult, such as subtleties in diagnosis and pathophysiology. The chapters are written by a distinguished group of international gastroenterologists and surgeons from Australia, Denmark, England, France, Germany, and Italy.

The book is organized into eight sections: oral cavity, esophagus, stomach and duodenum, small bowel, large bowel, rectum, liver, and pancreas. Each section covers one to three topics.

Topics that I found of interest included the chapters on refractory burning mouth syndrome, alimentary allergies resistant to conventional treatments, and refractory solitary rectal ulcer syndrome, since these sections were comprehensive and well organized. The chapter on refractory duodenal ulcer was quite complete and well referenced. I was surprised and somewhat disappointed that the book's treatment of inflammatory bowel disease did not include more information on the immunosuppressives—6-MP, azathioprine, cyclosporin—since I believe that these agents play an important role in treating patients who have refractory inflammatory bowel disease.

I agree with the editors that "the book lays no claim to being a comprehensive study of refractoriness in gastroenterology", but I did enjoy reading this text. I feel that the book would be an asset to postgraduate students interested in gastrointestinal diseases, internists, gastroenterologists, and gastrointestinal surgeons who are searching for answers to why patients may not respond to medical treatments.

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Mount Sinai School of Medicine

Instructions for Authors

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Introduction

Edward J. Bottone, Ph.D.
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Contemporary Protozoal Pathogens

This collection of articles dealing with free-living amebas of the genera *Acanthamoeba* and *Naegleria,* the leptomyxid ameba, and microsporidia is adapted from presentations at the Workshops in Clinical Lab Sciences Continuing Education Program, "Contemporary Protozoal Pathogens," held on October 25, 1991 at the Mount Sinai School of Medicine in New York.

The workshop was indeed special and arose as a consequence of a paucity of information, among laboratorians and clinicians alike, about the basic biology, epidemiology, pathogenesis, clinical presentation, and treatment of free-living ameba infections. The concept for the program began about a year before this workshop, when Penny Asbell, an ophthalmologist at Mount Sinai specializing in corneal infections, saw a patient she suspected of having *Acanthamoeba* keratitis and asked the Clinical Microbiology Laboratories to process corneal scrapings in search of this particular microorganism. The fact was that little microbiologic expertise could be brought to bear on her request. Furthermore, she suggested cocultivating the corneal scrapings with the bacterium *Escherichia coli* as a food source. Additionally, she suggested that we send the patient's contact-lens care system to Govinda S. Visvesvara at the Parasitic Diseases Branch of the Centers for Disease Control for isolation of any *Acanthamoeba.* Not realizing that Visvesvara is a world expert on free-living ameba, we deferred Penny Asbell's request and I was unsuccessful in recovering *Acanthamoeba* from the corneal scrapings or contact-lens case.

Subsequently, a second patient came to The Mount Sinai Hospital with keratitis presumed to be caused by *Acanthamoeba.* In this instance, Dr. M. Nasar Qureshi and I were able to demonstrate the organism in Giemsa-stained smears of corneal scrapings and in direct preparations of the patient's contact-lens care system. For us these findings were stimulating and ushered in a whole new entity of diagnostic and academic interest. With that in mind, I judged that if at Mount Sinai there was such a paucity of information on the basic microbiologic attributes of this microorganism, a discussion of *Acanthamoeba* might be a good topic to bring to an audience of colleagues and peers in New York City. Thus, with such naivete, I approached the codirectors of the continuing education workshops, Victor D. Bokkenheuser, Marcelino F. Sierra, and Yvonne Lue, and we decided to organize this program.

I was assigned the responsibility of securing the various speakers and promptly called Dr. Visvesvara at the Centers for Disease Control, who agreed to participate. Because I was interested in adding discussions of other clinical topics in addition to keratitis, he suggested I contact A. Julio Martinez, a neuropathologist at the University of Pittsburgh School of Medicine, who eagerly agreed to participate. I rounded out the program by inviting Penny Asbell to discuss *Acanthamoeba* keratitis.

I then embarked on a literature search and was both astounded by the flourishing interest in *Acanthamoeba* and *Naegleria* and dazzled by the numerous pioneering contributions, dating back to 1970, by Visvesvara and Martinez to our understanding of various laboratory, epidemiologic, and clinical correlates of *Acanthamoeba* and *Naegleria* infections.

In assembling these discussions I can attest to the joyful experience M. Nasar Qureshi and I have had in working with *Acanthamoeba;* it is a fascinating entity of significance, especially with cases of pneumonitis and cerebral involvement being described in the setting of AIDS.

I hope these discussions will bring a greater appreciation for these primitive but provocative protozoal species.

Free-Living Amebas of the Genera *Acanthamoeba* and *Naegleria:*

An Overview and Basic Microbiologic Correlates

Edward J. Bottone, Ph.D.

THE MAJOR GENERA containing the pathogenic free-living amebas are listed in Table 1. Several species of *Acanthamoeba* produce human infection, of which *A. astronyxis, A. castellanii, A. culbertsoni,* and *A. polyphaga* are the most common. Only one species of *Naegleria, N. fowleri,* has been associated with human disease, namely, a fulminating meningoencephalitis (1–3). *N. australiensis* (4, 5) and its subspecies *italica* (6) have been shown to produce meningoencephalitis in animal models that histologically mimics that produced by *Acanthamoeba* and *N. fowleri* in human hosts. Although neither of these *Naegleria* species has been implicated in human disease to date, there is a potential for these amebas to join the ranks of *N. fowleri* with regard to human pathogenicity. Most recently, Visvesvara and colleagues (7) described an ameba of the order Leptomyxida of soil origin which can cause amebic meningoencephalitis in humans and animals.

The life cycle of free-living amebas is comprised of the active trophozoite and a dormant cyst form; in addition, in *Naegleria* there is a transient flagellated form during its life cycle (Table 2). The trophozoites of both species are morphologically distinct; they have a nucleus with a central nucleolus and divide by binary fission (Fig. 1), using a mitotic process. The *Acanthamoeba* trophozoite is further distinguished by the presence of fine filamentous projections called acanthopodia arising from the cytoplasmic membrane. Cytoplasmic vacuoles may also be prominent. The cyst form resists dessication and allows the organisms to persist in nature. The cyst is distinguished by outer (ectocyst) and inner (endocyst) walls that communicate by a pore that has a mucoid plug called an operculum (8). In *Acanthamoeba* the ectocyst wall is polyhedral and the endocyst is corrugated (Fig. 2), whereas the outer cyst wall in *Naegleria* is smooth (7). The factors that control encystment and excystment are not known. Generally, adverse environmental conditions induce the trophozoites to encyst, most probably through a series of complex biochemical events.

Speciation of *Acanthamoeba* is based on cyst-wall morphology encompassing size and shape and the distance separating ectocyst and endocyst wall (9). Because cyst morphology within a single species may vary according to cultural conditions, for example monaxenic versus growth media supplemented with $MgCl_2$ (10), other characteristics have been used for species identification of *Acanthamoeba,* including isoenzyme profile (11) and restriction fragment length polymorphism (RLPs) of mitochondrial DNA (12, 13).

Ecologically, free-living amebas are ubiquitous in the environment. *Naegleria* species prefer natural and artificially heated aquatic and soil environments (3, 14), whereas *Acanthamoeba* pervade the entire environment (Table 3). Two sources from which *Acanthamoeba* have been isolated, tap water and contact lens cases, bear directly on the pathogenesis of ameba keratitis.

Adapted from the author's presentation at the Workshops in Clinical Lab Sciences Continuing Education Program, "Contemporary Protozoal Pathogens: *Acanthamoeba, Naegleria,* Leptomyxid Ameba, and Microsporidia," at the Mount Sinai School of Medicine, New York, NY, on October 25, 1991. Final revision received March 1993. From the Clinical Microbiology Laboratories, The Mount Sinai Hospital. Address reprint requests to the author at Box 1122, Mount Sinai Medical Center, One Gustave L. Levy Place, New York, NY, 10029.

Further, *Acanthamoeba* species, as well as other free-living amebas, have also been isolated from eyewash stations (15). As a consequence of this organism's broad distribution in water, sand, soil, dust, especially in the resistant cyst form, human contact is constant and probably accounts for the widespread prevalence of antibody to *Acanthamoeba* and even to *Naegleria* (16) in human sera.

Human Infections

The major human infections caused by free-living amebas of the genera *Acanthamoeba* and *Naegleria* are shown in **Table 1.** Although *N. fowleri* produces only one devastating infection, the rare but highly fatal primary amebic meningoencephalitis (PAM), which follows exposure to amebas in heated water (3, 17), *Acanthamoeba* species are more versatile in their human disease potential. Indeed, *Acanthamoeba* can also invade the central nervous system to produce granulomatous amebic encephalitis (GAE), predominantly in debilitated hosts. In this setting, however, the clinical manifestations of a subacute, diffuse, necrotizing, granulomatous encephalitis differ significantly from the acute naeglerial meningoencephalitis. The route of acquisition appears to be by hematogenous spread of *Acanthamoeba* from either a pulmonary or cutaneous focus (18), rather than through the nasal mucosa and along the olfactory tracts with eventual invasion of the subarachnoid space, as in naeglerial meningoencephalitis (19–21).

TABLE 1
Free-Living Amebas and Human Infections

	Human infections	Virulence properties
Acanthamoeba	Granulomatous amebic encephalitis	Adhere to mucosal surfaces
A. astonyxis	Keratitis	Migrate through tissue @ 37°C, 28°C
A. castellanii	Pneumonitis	
A. culbertsoni	Granulomatous dermatitis	Cytopathic enzymes elastase, protease, collagenase
A. polyphaga	Isolated from: ear, nasopharynx, maxillary sinus, mandibular autograft, stools	
Naegleria	Primary amebic meningoencephalitis	Adhere to mucosal surfaces
N. fowleri		Migrate through tissue @ 37°C
*N. australiensis**		Cytopathic enzymes elastase, protease
*N. australiensis ssp. italica**		
N. gruberi		
		Phagocytosis of host neutrophils
Leptomyxid ameba		

* Produces in mice subacute meningoencephalitis comparable to that caused by *Acanthamoeba* spp.

Diagnostically, in PAM, *Naegleria* trophozoites are abundant in brain tissue and cerebrospinal fluid, whereas in GAE, *Acanthamoeba* trophozoites and cysts are easily seen in histologic sections, but *Acanthamoeba* trophozoites are absent from cerebrospinal fluid (22). Recently, *Acanthamoeba* central nervous system infection has increased in the setting of the acquired immunodeficiency syndrome (23–26). *Acanthamoeba* have also caused disseminated infections involving the skin (27). Other sites of involvement include the sinuses (23, 24), nasopharynx (28), external ear canal (29), gastrointestinal tract (30), and autogenous mandibular bone graft (31).

Acanthamoeba keratitis is now the most heralded of human infections, occurring in an increasing number of individuals predominantly in association with daily wear of soft contact lenses (32). Since the first reported case of *Acanthamoeba* keratitis, documented in 1973 (33), numerous case reports have appeared, and the topic has been extensively reviewed by Auran et al. (34) and Asbell (35).

The role of *Acanthamoeba* in keratitis is undisputed and is substantiated mainly by human clinical cases and by animal experimentation (36). Despite these revelations, however, the exact pathogenesis of human eye infection remains unresolved. In the nonwearer of contact lenses, antecedent minor corneal trauma is thought to be a prerequisite to *Acanthamoeba* keratitis. Because most of these infections occur during warmer weather, often subsequent to water exposure (34), it is theorized, but unproven, that the amebic trophozoite is the infectious form.

In the contact-lens wearer, the pathogenesis of amebic keratitis is also unresolved, although John and colleagues (37) have offered a plausible sequence of events. In their opinion, on exposure of the contact lens to solutions containing *Acanthamoeba,* cysts and trophozoites almost immedi-

TABLE 2
Life Cycle of Acanthamoeba*

Trophozoite
Single nucleus; large, dense, central nucleolus
Flat, irregular, produce slender pointed micropseudopodia (acanthopodia)
Divides rapidly by binary fission (mitosis)

Cyst form
Single nucleus; central nucleolus; polyhedral, convex, double-walled cyst
Outer, ectocyst
Inner, endocyst
Cyst walls communicate through pores containing a plug, operculum

* During life cycle of *Naegleria*, a transient pear-shaped biflagellate stage is produced. Cysts are smooth-walled.

TABLE 3
Ecology of Acanthamoeba

Free-living ameba present in all types of environments throughout world.
Cyst form resistant to disinfection and dessication.
Isolated from:
  Fresh water, seawater, ocean sediment, swimming water.
  Tapwater, bottled mineral water.
  Industrial cooling water, air conditioners.
  Air, sewage, soil, compost, dust.
  Chlorinated swimming pools, physiotherapy pools.
  Dental treatment units, dialysis units.
  Contact lens cases. Eye wash stations
  Vegetables, fish, reptiles, birds.

ately adhere to the lens surface. This is true even for unworn contact lenses, extended-wear lenses, and disposable soft contact lenses (38). In this setting *Acanthamoeba* may persist if the lens is not optimally disinfected. Placement of the lens on the eye surface allows amebas to become established in the conjunctival flora and brings *Acanthamoeba* into close proximity to the corneal stroma. Minor corneal irritation or abrasion may allow corneal penetration of the amebas.

The mechanism proposed by John et al. (37) to account for ameba keratitis gives little consideration to the role of contaminating microflora in the eye itself or in the contact lens care system as a major cofactor in the provision of numerous ameba trophozoites as a prelude to corneal invasion.

At The Mount Sinai Hospital, we encountered a patient with ameba keratitis whose contact lens care system was cocontaminated with an *Acanthamoeba* and numerous bacteria that proved on culture to be *Xanthomonas maltophilia.* Of striking interest on gram-stained smears of the solution was the presence of numerous *Acanthamoeba* trophozoites encircled by a ring of gram-negative slender rods, many internalized in phagocytic vacuoles (**Fig. 3**). Investigation of the role of bacterial cocontaminants in contact lens care systems as substrates for the growth of *Acanthamoeba* revealed that *Acanthamoeba* trophozoites readily feed on bacterial cocontaminants deriving from aquatic and soil environments cohabitated by amebas (39). These bacterial species include *X. maltophilia, Flavobacterium breve,* and *Pseudomonas paucimobilis,* which are common contaminants of contact lens care systems (40, 41). Thus, the nature of the bacterial cocontaminants in the contact lens case either promotes or abates *Acanthamoeba* growth, a fundamental principle underscoring *Acanthamoeba*-induced keratitis.

In the presence of a suitable bacterial food source, *Acanthamoeba* cysts undergo excystment (42), freeing the predatory trophozoite form, which then feeds on the bacterial substrate and multiplies to large numbers (**Fig. 4**). Attachment of *Acanthamoeba* trophozoites and cysts to the contact lens itself (37, 38) now apposes numerous amebas contiguous to the corneal surface poised for invasion subsequent to a minor corneal insult. The end result of these ameba-bacterial interactions, initiated in the ecologic niche of contact lens care system, is clinically apparent keratitis.

Virulence

The attributes of free-living amebas contributing to virulence in human infection are listed in Table 1. Initially, as with any microbial infection, adherence of the offending microbe to the target epithelium is a prerequisite for infection. *Acanthamoeba* have been shown to adhere not only to inanimate surfaces (37, 38) but also to corneal epithelium (43), a characteristic which increases with time (120 min) and incubation temperature (37°C) (44). Interestingly, *Acanthamoeba* species may show interstrain differences in adherence to corneal epithelium, a correlate which may underscore the increased incidence of specific *Acanthamoeba* species, especially *A. polyphaga* and *A. castellanii,* in keratitis (44).

Migration patterns of *Acanthamoeba* and *Naegleria* through tissue may also account for differences in clinical presentation of disease and for the epidemiologic circumstance surrounding acquisition of a pathogenic free-living ameba. *N. fowleri,* the causative agent of PAM, a rapidly fatal meningoencephalitis, is often acquired by swimming in contaminated warm waters. Infection occurs when the nasal mucosa is exposed to the trophozoite form of this ameba, which then penetrates the nasopharyngeal mucosa, migrates along the olfactory nerves, and invades the brain through the cribiform plate. At 37°C, *N. fowleri* trophozoites exhibit rapid locomotion, which aids their invasive potential (45), whereas nonpathogenic *Naegleria* species, such as *N. gruberii,* migrate poorly at 37°C but are more active at 28°C.

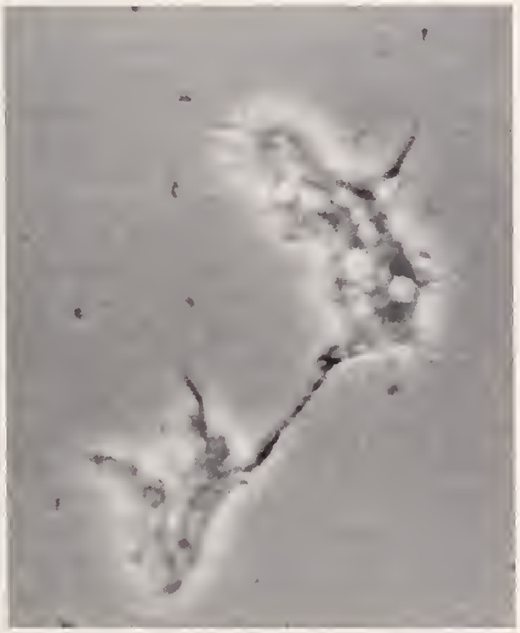
Consequently, *N. fowleri* produces one major human disease, whereas *Acanthamoeba* induces a broader clinical spectrum, including cutaneous lesions (27). Furthermore, the epidemiology of *Acanthamoeba* brain involvement, granulomatous amebic meningoencephalitis, is different from that of *Naegleria*. Indeed, *Acanthamoeba* cerebral infection occurs in the absence of exposure to contaminated water by hematogenous spread from a cutaneous or pulmonary focus (46). Perhaps the cutaneous propensity reflects the predilection for *Acanthamoeba* to migrate better at lower (28°C) than at higher (37°C) temperatures.

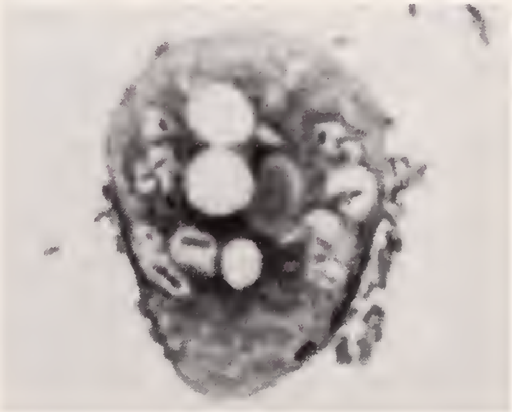
Penetration of mucosal surfaces subsequent to adherence and colonization is an essential step in the invasive process of free-living amebas. To achieve tissue invasion, *Naegleria* and *Acanthamoeba* species have been shown to elaborate several cytopathic enzymes, such as phospholipase A, sphingomyelinase, protease, and an elastase (47). Analogous to human leukocyte elastase, the amebic enzyme degrades connective tissue proteins such as fibrinogen, collagen, and proteoglycan. *A. castellanii* has additionally been shown to produce a collagenolytic enzyme that digests collagen shields and purified collagen and may contribute to corneal stromal degradation (48).

Phagocytosis of human neutrophils (49) and erythrocytes (50) through contact-dependent phenomena (analogous to the behavior of *Entamoeba histolytica*) may also underscore the pathogenicity, invasiveness, and virulence of free-living amebas. Phagocytosis of leukocytes and erythrocytes as well as cultured mammalian tissue (51) may be mediated through suckerlike structures (amoebostomes) observed by electron microscopy on the surface of *N. fowleri* (52).

Host Immune Responses

Despite the prevalence of free-living amebas in the human environment, few clinical cases





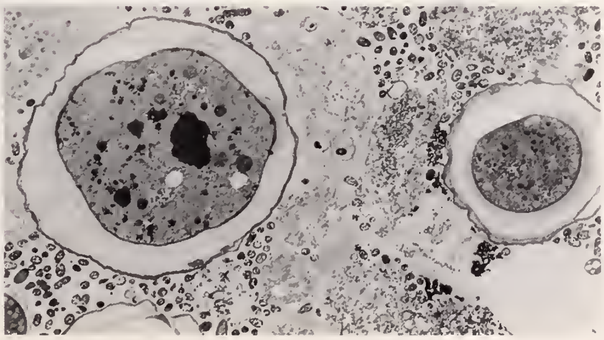


Fig. 1. Left Phase microscopy photomicrograph showing dividing *Acanthamoeba* linked by remnant of cytoplasmic membrane. **Fig. 2. Left below** Electron photomicrograph of *Acanthamoeba* cysts showing characteristic double-walled structure. Outer wall (ectocyst) is hexagonal, inner wall (endocyst) circumscribes the contour of ameba trophozoite (original magnification ×5200). **Fig. 3. Above** Gram-stained smear of contact lens care solution contaminated with *Acanthamoeba* and bacteria showing mantle of adherent gram-negative bacilli and some within phagocytic vacuoles in cytoplasm.

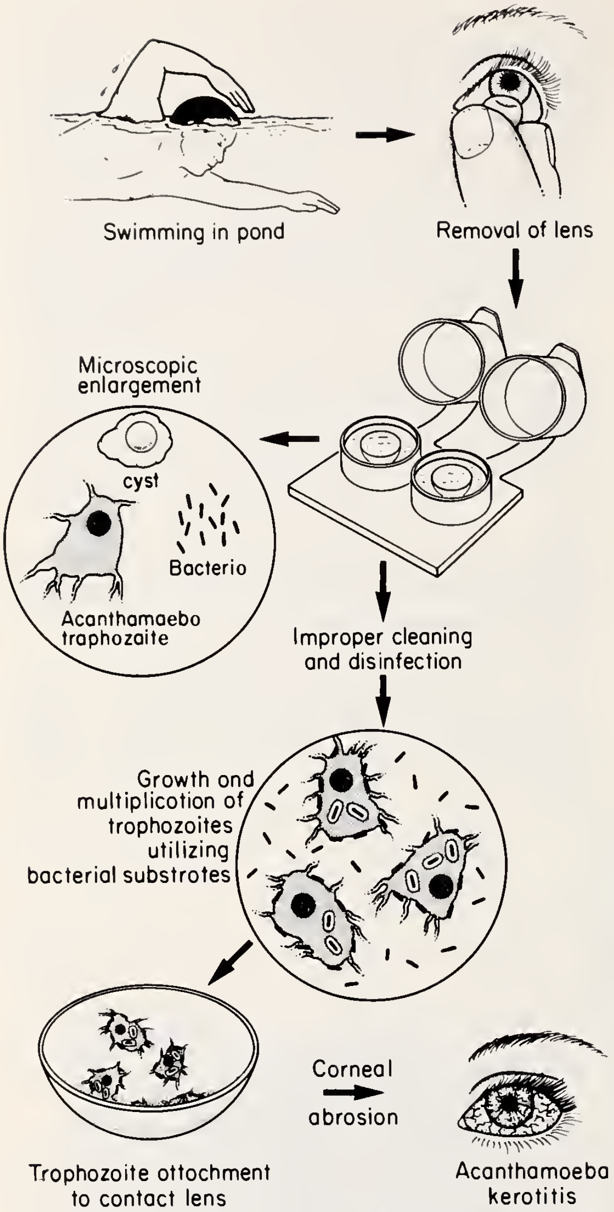

Swimming in pond
Removal of lens
Microscopic enlargement
cyst
Bacteria
Acanthamoeba trophozoite
Improper cleaning and disinfection
Growth and multiplication of trophozoites utilizing bacterial substrates
Corneal abrasion
Trophozoite attachment to contact lens
Acanthamoeba keratitis

Fig. 4. Role of bacterial cocontaminants in contact lens care systems leading to *Acanthamoeba* keratitis. Appropriate bacterial cocontaminants, usually from aqueous source, support growth of *Acanthamoeba,* leading to increased inoculum densities of cysts and trophozoites which can adhere to contact lens. Placement of lens over corneal abrasion facilitates ameba penetration of cornea, resulting in keratitis. *Reproduced with permission* from J Clin Microbiol 1992; 30:2447–2450. Original sketch courtesy of Robert M. Madayag.

have been described. Recorded clinical cases have occurred in the setting of immunosuppression (*Acanthamoeba*) (28), in immunologically deprived sites such as the cornea, or sporadically in previously healthy individuals, for example *Naegleria* meningoencephalitis. To account for the sparsity of free-living amebic human infections, several host defense mechanisms have been found operative (Table 4).

TABLE 4

Host Defense Against Acanthamoeba *and* Naegleria *Infections*

Serum antibodies
IgG, IgM; higher against *Naegleria;* elicited in response to environmental exposure to free-living amebas
Inhibit adherence of amebas to human tissue
Opsonizing

Complement activation
Alternative pathway
In vitro lysis of amebas in presence of C5-C9
Generation of iC3b on ameba membrane for recognition by phagocytes
Highly pathogenic *Naegleria fowleri* resistant to complement-mediated lysis even in presence of specific antibodies

Phagocytic cells (neutrophils)
Cytokine (TNF-α); altered neutrophils in presence of either antibody or complement
Neutrophils surround and adhere to ameba surface through pseudopod extension
Activation of:
  Oxidative respiratory system $O_2^- \cdot H_2O_2$
  Myeloperoxidase, H_2O_2, halide system

Complement-Mediated Lysis. Initially, in the nonimmune host, *Acanthamoeba* species may activate the alternative complement pathway, which leads to lysis of amebas (53). From a conceptual point of view it is interesting to speculate that this primitive defense mechanism may have evolved concomitant with, or in response to, the equally primordial one-celled ameba.

Although complement activation by *Acanthamoeba* may ensue through the classic antibody-mediated or the alternative pathway, there is no clear-cut evidence to support complement-mediated in vivo lysis of amebas (54). Indeed, according to Ferrante (54), it appears that the main function of complement activation is to generate opsonic factor iC3b to enhance phagocytic cell recognition of and attachment to amebas.

In contrast to *Acanthamoeba* and weakly pathogenic *Naegleria* species, highly pathogenic *N. fowleri* amebas are resistant to in vitro complement-mediated lysis (55). Thus, although pathogenic *N. fowleri* do activate complement, they may evade lysis by inhibiting the terminal steps of complement action, by shedding the membrane attack complex, or by internalizing and degrading the terminal complement components (55).

Serum Antibodies. Because of the ubiquity of free-living amebas, antibodies against these species are prevalent in human sera. In a study conducted in New Zealand (16), Cursons et al. found antibodies in all 93 serum samples tested with titers ranging from 1:5 to 1:20 for *Naegleria* species and from 1:20 to 1:80 for *Acanthamoeba* species. Antibodies belonged primarily to the immunoglobulin G (IgG) and immunoglobulin M (IgM) classes, suggesting both old and recent contact. Further, IgG antibodies were detected in cord sera of newborn infants, suggesting that antibodies to *Acanthamoeba* are transferred placentally. Cursons et al. (16) postulate that serum antibodies to *Acanthamoeba* may serve as opsonins enhancing phagocytosis of amebas, may prevent attachment of amebas to mucosal surfaces, can activate complement, and can agglutinate or immobilize amebas.

Serum antibodies have also been detected against *N. fowleri* and the nonpathogenic *N. gruberi.* Unlike antibodies to *Acanthamoeba,* agglutinating antibodies are negligible in infants' sera because these antibodies are of the IgM class and hence not passed transplacentally (56). Animal studies have shown that resistance to intranasal challenge by *N. fowleri* could be enhanced with immune sera, thereby supporting a role for antibody in immunity to this ameba species (57). Interestingly, *N. fowleri* may evade immune surveillance by removing antibody from its surface by redistributing, capping, and internalizing surface-bound antibody (58).

Neutrophils. In host immunity to free-living ameba infections, the neutrophil plays a central role. Early and elegant work of Ferrante and Thong (59) demonstrated that in immune mice, neutrophils surround, adhere to, and immobilize ameba trophozoites, and pinch off and ingest portions of the trophozoite, which then ruptures. Further, in support of the central role of the neutrophil, Ferrante and colleagues (60) showed that either abrogation of neutrophil function or depletion of neutrophils in immune mice markedly reduced immunity to pathogenic *Acanthamoeba* and *Naegleria.* Macrophages and lymphocytes from human peripheral blood are not in themselves effector cells against free-living amebas even in the presence of antibody (61, 62).

For human neutrophils to kill *Acanthamoeba* and *Naegleria* effectively, several other host defense parameters must be met. Initially, neutrophils must bind to the ameba trophozoite surface, a feat achieved in the presence of antibody or complement components mediating neutrophil attachment. Second, neutrophils must be activated by the cytokine tumor necrosis factor alpha (TNF-α), derived from stimulated macrophages (63).

In studies with *N. fowleri,* Ferrante and colleagues (64) showed that primed neutrophils kill amebas through enhancement of hypochlorite (HOCl) production through the myeloperoxidase H_2O_2-halide system, and enhancement of the oxidative respiratory system leading to increased superoxide anion production. In the presence of amebas opsonized by either antibody or complement, similar augmentation of neutrophil amebicidal activity by TNF-α has been demonstrated against *Acanthamoeba* (*A. culbertsoni*) as well (54).

TABLE 5

Diagnosis of Free-Living Ameba Infections

Direct staining of corneal scrapings/CSF
Giemsa
  Cysts clear, refractile, polyhedral, stellate.
  Trophozoite pale blue, uninucleate, may resemble macrophages
Gram
  Cysts poorly staining
  Trophozoites poorly staining
Fluorescent antibody (indirect)
Calcofluor white (fluorescent fabric brightener with affinity for chitin and cellulose [B-linked carbohydrates])
    Cysts, corrugated double wall, apple-green fluorescence; interior, orange-red
    Trophozoites counterstained by Evans blue a bright red-orange

Fluorescein-conjugated lectins
Glycoproteins that bind to carbohydrate moieties—Concanavalin A; cysts and trophozoites stained

Fixed-tissue stains
Hematoxylin-eosin
Periodic acid-Schiff
Gomori's methamine silver

Examination of contact lens
by light microscopy or by calcofluor staining; cysts easily visible

Examination of contact lens care system

Cultural methods
Nonnutrient agar plates with Page's ameba saline seeded with *Escherichia coli* or *Enterobacter aerogenes* (18–24 h old)
Scan agar surface for trophozoites and cysts (3 days incubation) for 7 days; trophozoites produce wave-like tracks
Filter-culture technique
  Specimen collected in ameba saline; filtered, 0.22 μm pore size; filter removed and placed on *E. coli* seeded plates
Amplification of ameba by direct addition of growth-promoting bacterial species to specimen/contact care system solution
Tissue culture, monkey kidney (vero) cytopathic effect, plaques

Animal inoculation
Two-week-old mice, nasal inoculation with ameba suspension

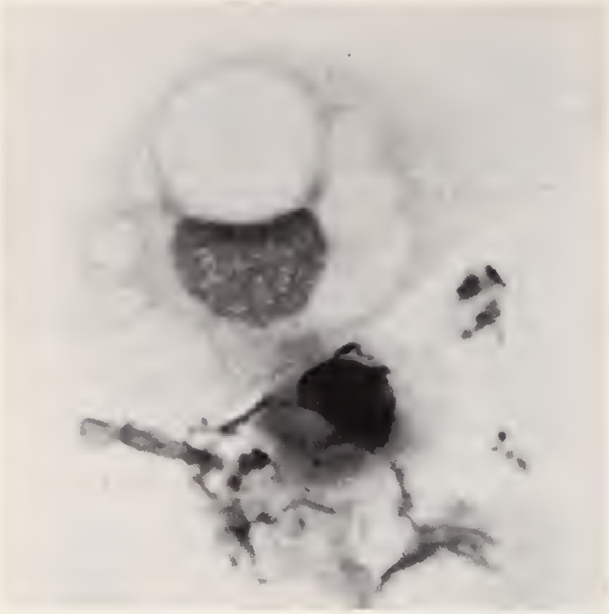


Fig. 5. Giemsa-stained smear of corneal scraping showing *Acanthamoeba* trophozoite distinguished by central dense nucleolus, numerous vacuoles, and ovoid ameba morphology.

Diagnosis

The diagnosis of *Acanthamoeba* or *Naegleria* infection requires an initial heightened index of suspicion for their presence. Whereas *Naegleria* may be suspected on epidemiologic evidence—for example meningoencephalitis following exposure to amebas in warm contaminated water—nonkeratitic *Acanthamoeba* infections require an awareness of the potential presence of *Acanthamoeba.*

Acanthamoeba keratitis is the most commonly recognized presentation of this free-living ameba. Diagnosis ensues from an initial index of suspicion through a variety of staining, histologic, and cultural modalities (64a) **(Table 5).** Animal inoculation is rarely utilized.

Standard Staining Techniques. When *Acanthamoeba* keratitis is suspected, the ophthalmologist should alert the microbiologist and should forward to the laboratory corneal scrapings and the patient's contact lenses and contact lens storage system to be microbiologically evaluated for *Acanthamoeba* (65). At the outset, corneal scrapings may be examined after staining by the Gram and Giemsa methods. The former is of value in ruling out a bacterial or fungal cause of the corneal ulcer; the latter may be used to detect multinucleated giant cells and intranuclear inclusion, suggesting a viral (herpes, adenovirus) keratitis.

In gram-stained preparations *Acanthamoeba* trophozoites may be only faintly visible, although an uneven cellular contour due to pseudopod extension and a nucleus with a central nucleolus are readily visible. Further, food vacuoles may be discerned in the trophozoite cytoplasm. In our laboratory, basic fuchsin is used as the gram counterstain, and by overstaining the corneal smear for two minutes, ameba trophozoites are more readily discerned. Careful search should also be made for the copresence of *Acanthamoeba* cysts delineated by their double-walled stellate morphology.

In Giemsa-stained corneal scrapings, *Acanthamoeba* trophozoites are pale lavender, irregular, and surrounded by a clear halo **(Fig. 5).** Although difficulty may be encountered in differentiating trophozoites from mononuclear and epithelial cells, careful attention to nuclear morphology (irregular and kidney-shaped in monocytes), the presence of large food vacuoles, and extending pseudopodia may aid *Acanthamoeba* differentiation. In this staining technique *Acanthamoeba* cysts are clear, refractile, and either faintly stained or unstained (66). Other staining techniques used with variable success in detecting *Acanthamoeba* include hematoxylin-eosin, periodic acid-Schiff, Gomori's methamine silver, Wright's stain, methylene blue, congo red, Janus green, Masson stain, and Wheatley's trichromes, and acridine orange.

Newer Staining Techniques. Because of the inherent expertise required for the recognition of *Acanthamoeba* directly in corneal scrapings through evaluation of standard staining techniques, several newer techniques that enhance the visualization of *Acanthamoeba* trophozoites and cysts have been described. One makes use of calcofluor white (67), a fluorescent brightener with a strong affinity for chitin and cellulose, polymers of B-linked polysaccharides. Initially used to stain cell walls of fungi containing these compounds, calcofluor white stains the amebic cyst wall a fluorescent green while the protoplasm stains red-orange (67). Evans blue is used to counterstain background epithelial and inflammatory cells as well as the ameba trophozoite a bright red-orange (67, 68). Because of the affinity of calcofluor white for chitin, cysts are more readily detected than the amebic form (69). Calcofluor white alone without counterstain has also revealed *Acanthamoeba* cysts adherent to the surface of a contact lens derived from a patient with suspected *Acanthamoeba* keratitis, thereby confirming the diagnosis (70).

Indirect fluorescent antibody staining of *Acanthamoeba* using species-specific hyperimmune antisera has been used mainly to identify

Acanthamoeba isolated from human infections (71). This technique has also allowed for the detection of *Acanthamoeba* trophozoites and cysts in various human and experimentally infected tissues (71, 72). A limitation of this technique is the unavailability of commercial antisera.

In an attempt to remedy the lack of a widely available technique to identify both forms of *Acanthamoeba*, Robin and colleagues (73) investigated a variety of fluorescein-conjugated lectins, such as concanavalin A and wheat germ agglutinin. Lectins are glycoproteins which bind specifically to carbohydrate moieties. Conjugating these compounds to a fluorescent dye facilitates their visualization when bound to the surface of cells (bacteria, fungi, ameba) containing appropriate lectin receptors. Each of the nontraditional staining methods have proven successful in demonstrating *Acanthamoeba* in deparaffinized histologic sections of corneal or other tissue biopsies.

Cultural Assays. Culturally, *Acanthamoeba* may grow alone on blood or chocolate agar, producing tracks across the agar surface (65). This cultural technique, however, is quite insensitive and in the absence of a clear suspicion of the presence of *Acanthamoeba* in the inoculated specimen, these tracks may be easily overlooked on plates discarded without microscopic examination of the agar surface.

To enhance cultivation of *Acanthamoeba* from corneal scrapings, it is recommended that the specimen be inoculated to a nonnutrient agar preseeded with either *Escherichia coli* or *Enterobacter aerogenes* (74). In this fashion an appropriate bacterial lawn is made available for the predatory ameba trophozoite to feed and grow on. Agar plates are then scanned by low-power (100×) microscope in a search for ameba trophozoites. Because *Acanthamoeba* are free-living, cocultivation with bacterial species derived from their natural environment, such as *Xanthomonas maltophilia, Pseudomonas paucimobilis* (but not *P. aeruginosa*) (74a), and *Flavobacterium breve,* which are also common contaminants of contact lens care systems (39, 40), enhances growth of *Acanthamoeba* species (39). Gradus et al. (75) have emphasized the value of filtering corneal scrapings inoculated to Page's ameba saline (74), placing the filter on a lawn of *E. coli,* and examining the medium daily by low-power microscopy for trophozoites.

Recently, Bottone and colleagues (76) described an amplification technique for the cultivation of *Acanthamoeba* from corneal scrapings and contact lens care systems. In this procedure, specimens are inoculated to tubes of sterile physiologic saline (2.5 mL), after which 0.5 mL of a fresh turbid suspension of *X. maltophilia* is added and incubated at 37°C. A drop of the cocultivation suspension is then examined at daily intervals by direct or phase contrast microscopy for the presence of, or increased number of, amebic trophozoites and cysts (**Fig. 6**). The advantage of this procedure over the agar method is that it obviates the low-power scanning of agar surfaces in search of ameba trophozoites which, in a liquid milieu, are more readily discerned as contrasted to the more restrictive agar surface. Whatever the cultural technique, the sensitivity of the assay is directly related to the clinical suspicion of the presence of *Acanthamoeba* (35).

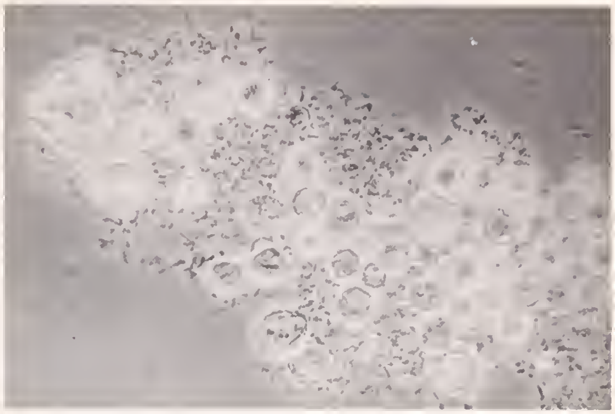


Fig. 6. Phase-contrast photomicrograph showing numerous *Acanthamoeba* cysts and trophozoites following amplification of growth in presence of *Xanthomonas maltophilia* bacterial food source.

In vitro tissue culture techniques using human corneal epithelial cells (77) or rabbit corneal fibroblasts (78) have also been described for the isolation of acanthamoebae but remain limited to research rather than routine use in laboratories.

Summary and Conclusions

Free-living amebas of the genera *Acanthamoeba* and *Naegleria* are allied in basic cell biology, ecology, and human disease-producing potential. However, several enigmas surrounding these amebas need further intellectual and scientific scrutiny. For instance, a clearer differentiation is needed of factors delineating pathogenic species—those most frequently associated with human infections—from nonpathogenic species. Further, have the pathogenic species bridged the gap in a step-wise fashion between their habitat and the human host to express their disease-producing potential?

Second, what attributes of amebas account for the spectrum of disease caused by *Acan-*

thamoeba and *Naegleria?* In the brain, *Naegleria* is highly destructive of tissue in the course of a rapidly evolving, hemorrhagic primary meningoencephalitis in normal individuals. Central nervous system invasion by *Acanthamoeba,* however, occurs only in compromised hosts, and is a more slowly evolving subacute to chronic encephalitis. Further, the epidemiology of the infections are disparate. *Naegleria* is acquired from exposure to contaminated fresh water; this epidemiologic link is absent in *Acanthamoeba* meningoencephalitis. *Naegleria* invades the central nervous system via the olfactory nerve; *Acanthamoeba* is deposited in the central nervous system via hematogenous spread from a pulmonary or cutaneous focus. Additionally, *Naegleria* is apparently restricted to the brain; *Acanthamoeba* is not so bridled, and invades more sites in the human body.

Finally, *Acanthamoeba* are beginning to appear opportunistically more frequently in patients infected with the human immunodeficiency virus. To avoid the same lack of effective therapeutics we still face in treating cryptosporidium infections in these patients, more emphasis must be placed on clinical trials dealing with the management of *Acanthamoeba* infections in patients with AIDS.

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Free-Living Amebas:

Infection of the Central Nervous System

A. Julio Martinez, M.D.

Abstract

Pathogenic free-living amebas of the genera *Naegleria* and *Acanthamoeba* and the leptomyxid ameba of the order Leptomyxida may be capable of producing disease in the central nervous system of human beings and animals. These amebas are distributed worldwide in thermally polluted streams, coastal and fresh water, dust, soil, and sewage, and heating, ventilating, and air conditioning units. *N. fowleri* may produce primary amebic meningoencephalitis, a rapidly fatal central nervous system infection. By contrast, the *Acanthamoeba* spp. and the recently described leptomyxid ameba may produce granulomatous amebic encephalitis, a protracted central nervous system disease, usually in immunocompromised hosts. The leptomyxid ameba may produce clinical symptoms similar to and histopathologic features almost identical to those in GAE. Contact-lens wearers may also develop *Acanthamoeba* keratitis, chronic ulceration of the corneal epithelium due to *Acanthamoeba* spp. The various central nervous system diseases produced by these free-living amebas result in divergent epidemiological patterns, diverse clinical manifestations, and distinct pathological features, and require different treatment.

THE STORY of free-living amebic infection has an interesting beginning. In 1930 Sir Aldo Castellani found and isolated a free-living, apparently harmless ameba growing in a yeast culture (1). In 1957 amebas were found to produce cytopathic effects on contaminated cell cultures (2). The disease caused by these amebas was first produced in laboratory animals in 1958 by Clyde Culbertson as a result of a fortuitous observation at the Eli Lilly Laboratory (3). Polio vaccine was being produced, and each batch was tested for safety on tissue culture plates. On one group of plates, plaques suggesting live virus appeared, and mice were inoculated with plate washings. The mice died from a meningoencephalitis, and detection of a possible nonattenuated virus was suspected. On further study, unusual cells were found in the brains of inoculated mice, and reexamination of the plates revealed a free-living ameba. It was identified as an *Acanthamoeba* spp., a common, small, free-living ameba noted to occur as an airborne contaminant of cell cultures in other laboratories (4). If not for the animal inoculations, the plaques would have passed as simply another instance of laboratory contamination.

The discovery that this presumably harmless free-living ameba, even when simply instilled into the nose, could invade the olfactory neuroepithelium, migrate to the brain, multiply in the subarachnoid space, invade the cerebral cortex, and produce a rapidly fatal meningoencephalitis was interesting and amazing. These important findings suggested the possibility of infection in humans and animals. These dramatic discoveries led to recognition of cases in humans in 1965,

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TABLE 1

Number of Cases Worldwide of Primary Amebic Meningoencephalitis (PAM) and Granulomatous Amebic Encephalitis (GAE) at September 1, 1991

Country	GAE	PAM	Total
Confirmed*			
Argentina	1	—	1
Australia	2	19	21
Belgium	—	5	5
Brazil	1	2	3
Canada	1	—	1
China	1	—	1
Colombia	1	—	1
Czechoslovakia	—	18	18
Great Britain	—	3	3
Honduras	2	—	2
India	3	1	4
Italy	1	—	1
Japan	2	—	2
Mexico	3	5	8
New Guinea	—	1	1
New Zealand	—	8	8
Nigeria	1	4	5
Panama	—	1	1
Peru	8	—	8
South Africa	1	—	1
South Korea	1	—	1
Thailand	—	2	2
United States	38	63	101
Venezuela	2	2	4
Zambia	1	—	1
Not confirmed†			
Barbados	1	—	1
Brazil	—	3	3
Cuba	—	1	1
Great Britain	—	3	3
Hungary	1	1	2
India	—	9	9
Mexico	—	3	3
Uganda	—	1	1
United States	1	1	2
Totals	73	156	229

* By autopsy, biopsy, or culture with isolation of amebas.

† Not confirmed by autopsy or culture of amebas.

when Fowler and Carter isolated *N. fowleri* from cerebrospinal fluid and reported the first case, from Adelaide, South Australia, and identified the responsible ameba in 1965 (5); however, what was originally described in this 1965 report as an *Acanthamoeba* spp. turned out to be *N. fowleri.* Cecyl Butt reported the first human case from Florida in 1966 and called the disease primary amebic meningoencephalitis (PAM) (6). In 1968 Callicott reported the first case from Virginia (7). In 1969 Symmers reported two cases from material kept in a museum in London; one of the two patients, from Essex, northeast of London, died in 1909, and the other, from Belfast, Northern Ireland, died in 1937 (8). In 1970 J. dos Santos retrospectively studied more than 400 cases of meningoencephalitis in Richmond, and found five additional cases, the earliest occurring in August 1937 (9).

There have been numerous reports of infection by *N. fowleri* (10–12) and by *Acanthamoeba* spp. (13–23). Recently a new species of free-living ameba, *Balamuthia mandrillaris* (23a), has been isolated, chiefly in patients with acquired immunodeficiency syndrome (AIDS) (24–28).

Classification and Protozoology

The free-living amebas comprise a group of ubiquitous protozoa belonging to the genera *Naegleria* (with a flagellate state) and *Acanthamoeba* and an ameba of the order Leptomyxida. They include several species of amphizoic amebas pathogenic to humans and animals. Amebas of the genus *Naegleria* are capable of producing a rapidly fatal, generalized meningoencephalitis, primary amebic meningoencephalitis (PAM). About 156 cases of PAM have been reported worldwide, 64 in the United States as of September 1, 1991 (Table 1). *Acanthamoeba* spp. and the leptomyxid ameba may produce a multifocal encephalitis, granulomatous amebic encephalitis (GAE). About 73 cases of GAE have been reported worldwide, 39 in the United States as of September 1, 1991 (Table 1). In addition, *Acanthamoeba* spp. may produce acanthamoebic keratitis, a chronic ulceration of the corneal epithelium. In this presentation some historical and protozoologic aspects, the clinical symptoms, diagnosis and pathologic features of free-living amebic infections will be discussed and compared (**Table 2**).

Naegleria. The amebas which have been isolated from humans are morphologically identical to the common, free-living *N. gruberi.* The trophozoites are active and usually elongated with broadly rounded, granule-free processes called lobopodia that erupt from the surface; granular cytoplasm flows into them. The cytoplasm is abundant with vacuoles. There is a conspicuous, clear nuclear halo and a dense, spherical nucleolus. When rounded, the trophozoite measures 10–15 μm in diameter (**Fig. 1**). The cysts are usually spherical, smooth, single-layered, and refractile. They measure about 10 μm in diameter. They have one or two small flat pores. *N. australiensis* is pathogenic to mice. The other species of *Naegleria* (*N. jadini, N. gruberi, N. lovaniensis*) have not so far been found to be pathogenic to human beings.

Acanthamoeba. The trophozoites of *Acanthamoeba* spp. (*A. castellanii, A. culbertsoni, A. polyphaga, A. palestinensis*) are recognized by slender, spinelike processes called acanthopodia. When rounded, the cells measure from 25 to 35 μm. Locomotion is by a slow, gliding movement. The cytoplasm is finely granular and usually contains a single nucleus which, like that of *Naegleria,* has a large, dense, central nucleolus surrounded by a clear nuclear halo. Water and food vacuoles are usually evident in the cytoplasm. The cysts are characterized by a double wall, are star shaped, hexagonal, polygonal, or spherical, and measure about 15 μm in diameter. They have two or more pores, opercula or ostioles.

Leptomyxid Ameba. The trophozoites and cysts of the leptomyxid ameba are similar to those of *Acanthamoeba* spp., having the same dimensions and fine structural details (24).

N. fowleri: Primary Amebic Meningoencephalitis

Pathogenesis and Epidemiology. The infection produced by *N. fowleri* is acquired by exposure to contaminated water in which the thermophilic strain of the pathogenic ameba multiplies.

Most patients with PAM are healthy, normal children or young adults; nearly all have fulminating illnesses rapidly leading to death; and the vast majority had been swimming or were otherwise exposed to stagnant water, or had inhaled dust or soil containing amebic cysts (12).

The olfactory neuroepithelium is the portal of entry and is the direct route of invasion by *N. fowleri.* The incubation period may vary from two to seven days in infected humans, and from 7 to 15 days in experimental animal infections. This, of course, may depend on the size of the inocula and the virulence of the amebas.

Swimming pools and artificial lakes are the principal habitat of *N. fowleri.* Warm water during the hot summer months, warm water near the discharge outlet of power plants, and poorly chlorinated warm swimming pools have been shown to facilitate the growth of the pathogenic *N. fowleri.*

Clinical Signs and Symptoms. The onset of clinical symptoms in PAM is usually abrupt and rapidly progressive, and consists of headache, fever, pharyngitis, or nasal obstruction or discharge. Occasionally an initial symptom is distortion of smell and taste. Headache, vomiting, and fever may persist, and then drowsiness, confusion, and stiff neck develop. Convulsions may also occur. Progressive deterioration follows, leading to deep coma but with minimal, if any, focal neurologic signs. The vast majority of patients die one to two weeks after the first symptoms appear.

Differential Diagnosis and Techniques. Free-living amebas should be suspected as etiologic agents in the differential diagnosis of every case of purulent (suppurative) meningoencephalitis in which bacteria are not found. Examination of the fresh CSF is mandatory because it may reveal motile amebas. The CSF of infected patients is cloudy and slightly hemorrhagic. It demonstrates increased cellularity composed chiefly of polymorphonuclear leukocytes, but without bacterial pathogens, and protein concentration is usually increased. Glucose content is normal or decreased. Ameba motility can be detected as the trophozoite undergoes alterations in shape and configuration. With wet preparations, motile amebas can be visualized in the CSF.

Smears of CSF may be stained with Wright or preferably with Giemsa. These techniques may reveal the characteristic trophozoites with sky-blue cytoplasm and delicate pink nuclei. Lymphocytes and monocytes have larger nuclei and scant cytoplasm. A history of good health in a child or young adult and a recent history of water-related sport activities are good clues for suspecting PAM (12).

Pathological Features. The significant histopathologic features in PAM have been confined to the CNS. Macroscopically, the brain shows severe edema characterized by narrowing of sulci and flattening of gyri with some herniations. A meningeal exudate is generally obvious in the basilar cisterns, but is minimal or nonexistent over the cerebral convexities, and is sometimes associated with focal hemorrhages on the cerebral cortex. The olfactory bulbs tend to be edematous, soft, friable, and often adherent to the adjacent cerebral cortex.

Microscopically, the purulent leptomeningeal exudate is composed of polymorphonuclear and mononuclear leukocytes with a variable number of amebic trophozoites (**Fig.** 2). The inflammatory reaction extends to the cerebral cortex, which shows variable degrees of inflammation, neuronal necrosis, edema, hemorrhages, and invasion with amebic trophozoites. The brainstem is also affected by the meningoencephalitic process, but shows less inflammatory change than do the cerebral hemispheres. Necrotizing angiitis is occasionally seen in PAM. Frequently, clusters of amebic trophozoites without inflammatory reac-

TABLE 2

Comparison of Naegleria *and* Acanthamoeba-*Leptomyxid as Organisms Causative of Disease*

	Naegleria fowleri	*Acanthamoeba*-Leptomyxid
Protozoology	Trophozoite: 10–15 μm diameter Round, conspicuous karyosome, clear nuclear halo. Lobopodia. Cyst: Round with pores. Mitochondria: Dumbbell shape. Divide by simple binary fission	Trophozoite: 25–35 μm diam. Mitochondria: Oval. Round, central karyosome, with clear nuclear halo. Acanthopodia. Cyst: Star shape with double walls.
Epidemiology	Good health previously. Recent history of swimming in lake or swimming pool. Hot summer months. 156 cases worldwide	History of poor health. Immunological incompetent patient AIDS. No history of swimming. 73 cases worldwide.
Incubation period	2–7 days humans; 1–2 weeks animals	Uncertain >10 days
Portal of entry	Olfactory neuroepithelium	Lung, skin, eyes
Onset	Acute, fast	Chronic, slow and insidious
Spread into CNS	Direct; amyelinic nervous plexus	Hematogenous
Organ affected	Brain	Lung, brain, eyes
Clinical course	Acute, fulminant	Chronic, usually prolonged
Signs and symptoms	Severe headache; anorexia, nausea, vomiting; fever (39–41°C), ataxia, diplopia, stiff neck, coma	Ataxia, cranial nerve palsies; mental abnormalities; hemiparesis; meningism; coma
CSF and lab data	CSF similar to bacterial meningitis but sterile. Neutrophilic pleocytosis. High protein. Low glucose. Direct examination of fresh CSF: trophozoites active and mobile. Cultivation-inoculation in mice	Consistent with viral
Pathology, host response, amebic forms	Acute purulent leptomeningitis. Hemorrhagic necrotizing meningoencephalitis. Marked brain edema. Perivascular collection of amebas. Only trophozoites in brain	Chronic granulomatous encephalitis with focal necrosis. Cysts and trophozoites in brain
Differential diagnosis	No distinct diagnostic differences from acute pyogenic (bacterial) meningitis	No distinct diagnostic differences from acute/chronic pyogenic (bacterial) meningitis, TB, fungal or viral encephalitis. Ocular: Herpes simplex or fungal keratitis
Therapy	Amphotericin B	Ketoconazol (Miconazol), sulfadiazine, propamidine isethionate (Brolene)

tion can be seen in the CNS. The amebic trophozoites follow a centripetal course of invasion, from cerebral cortex to the deep subcortical white matter. No amebic cysts are present in the CNS lesions.

Treatment and Prognosis. Except for supportive measures, such as control of temperature, fluid, and electrolytes, specific therapy in most cases has little influence on the natural course of PAM. Amphotericin B is the drug of choice for *N. fowleri* infections, but is of value only when given early in the course of the illness. Both amphotericin B and miconazole have been shown to be effective in vitro against *Naegleria* species.

Acanthamoeba spp. and Leptomyxid Amebas Granulomatous Amebic Encephalitis

The majority of patients with GAE are chronically ill, immunocompromised, and debilitated with other diseases or are undergoing immunosuppressive therapy and have no history of recent water-sports activities. Additional cases associated with AIDS should be expected (11–28).

Pathogenesis and Epidemiology. In GAE the route of invasion and penetration into the CNS appears to be hematogenous, probably from a primary focus in the respiratory tract (lung) or skin.

However, the amebas may also penetrate directly into the olfactory neuroepithelium. The lower respiratory tract, skin (skin ulcers), and eyes (corneal ulcers) appear to be the sites of primary lesions in patients who have *Acanthamoeba* spp. and leptomyxid ameba infections. Experimentally, an amebic pneumonitis due to *Acanthamoeba* spp. has been reported.

The infection produced by *Acanthamoeba* spp. and the leptomyxid ameba are probably opportunistic in the majority of cases. Patients with AIDS are particularly vulnerable. *Acanthamoeba* spp. and the leptomyxid ameba are also widespread protozoa that can be found as normal flora in healthy individuals and can be isolated from samples of fresh water, air, soil, bottled mineral water, and even from dialysis machines and air conditioning units.

The incubation period is probably more than 10 days and the clinical course is subacute and chronic, usually protracted, lasting several weeks.

Clinical Signs and Symptoms. The clinical symptoms are mental abnormalities and meningism with localizing neurological signs, and eventually coma and death.

Differential Diagnosis and Techniques. Retrospective diagnosis of free-living amebic infections has been made by studying microscopic slides from CNS tissues. In such instances identification of the responsible amebas has rested chiefly on immunologic studies of either sera or postmortem tissues, on morphologic features such as size and shape of trophozoites, and on the shapes of the cysts as noted in formalin-fixed and paraffin-embedded tissue. Immunofluorescent-antibody and immunoperoxidase techniques have been used, as well as electron microscopy.

The distinction between PAM and GAE is not difficult, especially in histologic preparations of infected tissues. In tissues the trophozoites of *Naegleria* measure approximately 10–15 μm, whereas those of *Acanthamoeba* are larger. Cysts with a wrinkled double wall in tissue are found only in infections with *Acanthamoeba* spp. and the leptomyxid ameba.

A distinctive feature of *N. fowleri* is its ability to convert into a flagellate form which can be induced by diluting the culture with water. In CSF, the amebas are easily confused with leukocytes but can be identified using an unstained wet preparation. By this method, the trophozoites can be seen to contain a single central or eccentric nucleus with a conspicuous karyosome and characteristic lobopodia.

Brain biopsy may be done for a diagnosis, particularly when a brain abscess, brain tumor or any other space-occupying mass, or a viral encephalitis is suspected.

Pathologic Features: Central Nervous System. The pathologic lesions in GAE may be present in the brain, the eyes, the lungs, or the skin. The cerebral hemispheres are usually characterized by mild, focal edema with areas of softening associated with necrosis and recent hemorrhage. There is flattening of the gyri and narrowing of the sulci only in the affected areas. The rest of the cerebral cortex is unremarkable. Bilateral uncal notching and cerebellar tonsillar herniation may be present, but they are inconspicuous. The posterior fossa structures, diencephalon, thalamus, and brainstem are usually the most affected areas. On CT scan the lesions may resemble a space-occupying mass, brain tumor, brain abscess, or hemorrhagic infarct.

The leptomeninges, mainly over the most affected cortical areas, are opaque and might reveal a moderate amount of purulent exudate and vascular congestion. The rest of the leptomeninges are transparent with normal vascularity. The olfactory bulbs and spinal cord are spared. The modest chronic inflammatory exudate covering the cortical gray matter is composed of lymphocytes, monocytes, plasma cells, histiocytic elements, and few, if any, polymorphonuclear leukocytes.

Angiitis with necrotizing arteritis and fibrinoid necrosis may be seen. The invading amebic trophozoites and cysts take a centrifugal course, usually from deep gray or white matter areas to the brain surface.

Trophozoites and cysts are the amebic forms observed, scattered throughout the lesions, but preferentially located in perivascular spaces and invading blood vessel walls (**Fig.** 3).

The majority of the lesions of GAE are characterized by a chronic and granulomatous reaction, with multinucleated giant cells. Some patients under immunosuppression may not have granulomatous inflammation because of the impaired immune system.

Pathologic Features: Eyes. In patients who have *Acanthamoeba* keratitis, the acanthamoebic trophozoites and cysts may also be identified in direct smears from the surface of the corneal ulcerations, and may be cultured from these materials.

Pathologic Features: Lungs. Amebic trophozoites and cysts may be present within the pulmonary alveoli encompassed by modest mononuclear cell infiltrate. These features are

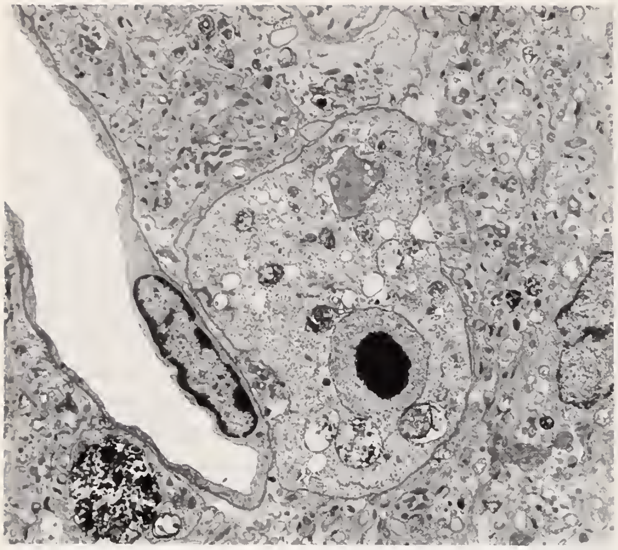

Fig. 1. Trophozoite of *Naegleria fowleri* within brain of experimentally infected mouse, inoculated intranasally with 10,000 trophozoites per cubic mL. Trophozoite is in close contact with blood vessel. Dense nucleolus is encompassed by finely granular nuclear chromatin. Cytoplasm contains empty vacuoles, lysosomes, mitochondria, and engulfed dense axoplasmic nests (electron micrograph; original magnification ×5,000).

characteristic of acanthamoebic pneumonitis. From the lower respiratory tract, amebic trophozoites and cysts may reach the CNS by hematogenous spread.

Pathologic Features: Skin. Among the reported cases of GAE, several patients had ulcerations or nodular lesions of the skin in which *Acanthamoeba* spp. were found on skin biopsies. This finding suggests a possible portal of entry of the protozoa which can reach the CNS by the hematogenous route. The skin lesions, particularly if not ulcerated, may also represent a terminal hematogenous dissemination of the protozoa, forming multifocal subcutaneous inflammatory foci and abscesses without disruption of the epidermis.

Treatment and Prognosis. Ketoconazole and clotrimazole are effective against some strains of *Acanthamoeba* spp. in vitro. Propamidine isethionate has been used with success to treat acanthamoebic keratitis. Sulfadiazine appears to be less active against *Acanthamoeba* spp.

Summary

The prognosis for patients who have the neurological disease produced by free-living amebas is generally poor. Effective management of PAM and GAE will depend on the development of curative drugs, on increased awareness of free-living amebic infections, and on methods of early diagnosis.

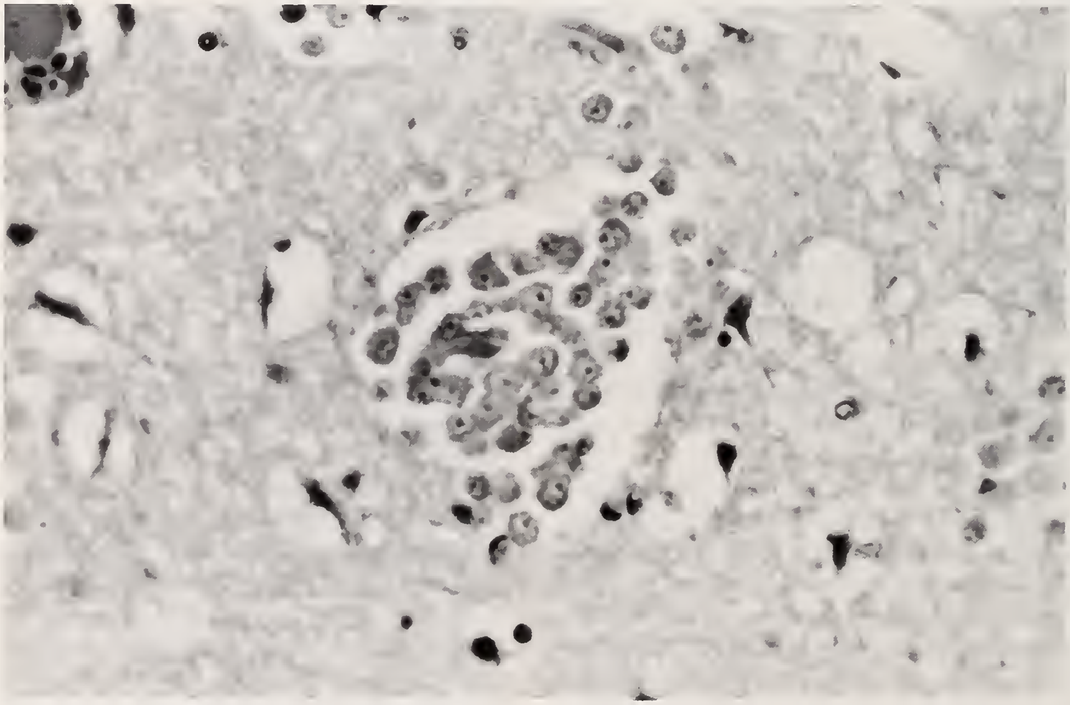

Fig. 2. Trophozoites of *Naegleria fowleri* within a Virchow-Robin space in patient with PAM. No accompanying inflammatory exudate. Neuropil is edematous and neurons are shrunken and ischemic (H&E; original magnification 400×).

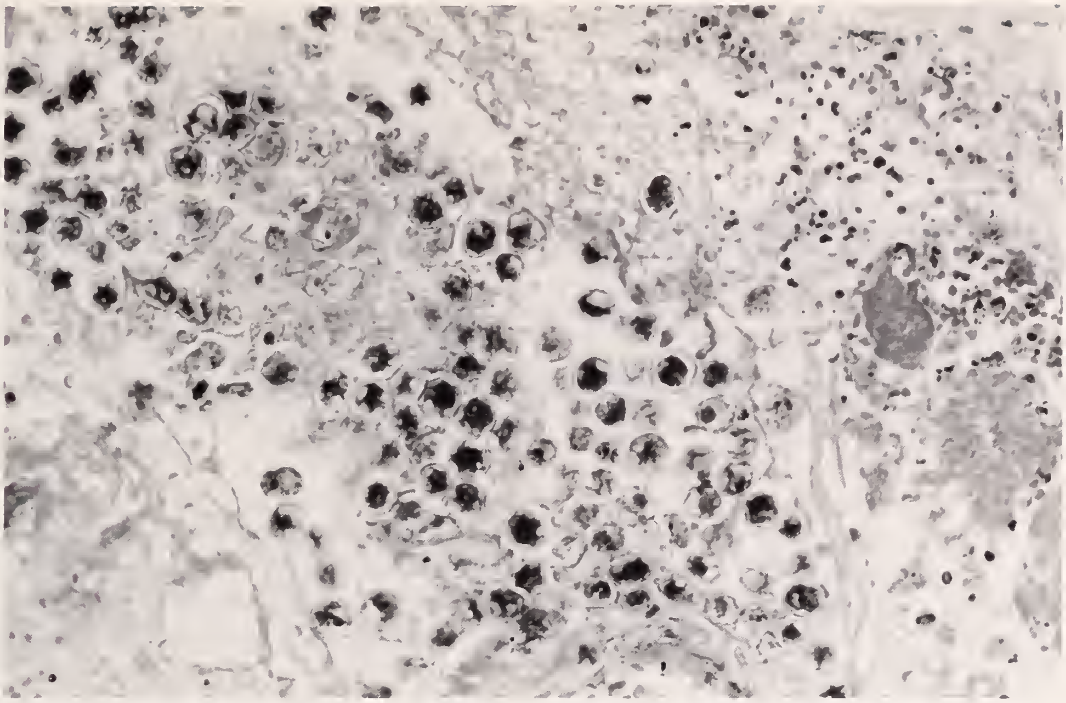

Fig. 3. Trophozoites and cysts of *Acanthamoeba castellanii* within area of necrotizing hemorrhagic encephalitis in occipital lobe in patient with GAE (H&E; original magnification 400×).

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Acanthamoeba Keratitis: There and Back Again

Penny A. Asbell, M.D.

Acanthamoeba keratitis is cause for serious concern to ophthalmologists. Its diagnosis and treatment are difficult. Moreover, the infection can cause permanent impairment of vision, and even blindness.

Corneal trauma is a precondition for ocular acanthamoebal infection. Even minor trauma caused during the insertion, removal, or normal wearing of contact lenses can provide an avenue for entry of the microorganisms. Whatever the environmental sources of acanthamoebae, which are numerous, the organisms enter the cornea and, depending on their number and virulence, produce clinical infection.

In 1973 Visvesvara reported the first case of *Acanthamoeba* infection of the eye (1). Few reports of ocular acanthamoebal infection followed; in 1982, not a single case of *Acanthamoeba* keratitis was found in a 30-year review of 700 patients with corneal ulcers, all of whom had undergone laboratory evaluation (2). Moreover, this study did not point to contact lenses as a risk factor. It was not until about 1985, after contact lens use had dramatically increased, that the direct association between contact lens wear and *Acanthamoeba* keratitis was recognized (3, 4).

Diagnosis

The common clinical signs and symptoms of ocular acanthamoebal infection are breakdown of the corneal epithelium, the presence of satellite lesions, and iritis, sometimes with hypopyon. Often, after an initial period of virulence, the infection progresses slowly. Diagnosis is complicated by the fact that the infection waxes and wanes, with corneal healing followed by recurrent epithelial deterioration. There may also be elevated intraocular pressure and scleral inflammation.

The classic initial sign of acanthamoebal infection that has penetrated deep into the cornea is the combination of a central or paracentral ring infiltrate and remarkably intense pain. Although the degree of pain seems disproportionate to the clinical signs, it becomes less surprising when one considers that the cornea has the highest density of free nerve endings in the body.

One method of diagnosis is to take corneal scrapings for culture and microscopic examination. Special staining and culture techniques can be useful. In some cases, biopsy may be necessary to obtain a firm diagnosis. In any event, it is most important, as Auran (5) pointed out, that specimens be examined by someone who is thoroughly familiar with the appearance of acanthamoebae.

Treatment

Initially, most patients required surgical treatment, the most drastic procedure being corneal transplantation. For example, Cohen et al. reported, in 1985, two cases of *Acanthamoeba* keratitis in which corneal transplantation was necessary for both diagnosis and treatment (6), and, in 1987, five cases treated by penetrating keratoplasty (7).

Wright reported the first successful medical treatment of *Acanthamoeba* keratitis (8). He used neomycin and Broline, a combination of dibromopropamidine and propamidine isethionate, which

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Adapted from the author's presentation at the Workshops in Clinical Lab Sciences Continuing Education Program, "Contemporary Protozoal Pathogens: *Acanthamoeba, Naegleria,* Leptomyxid Ameba, and Microsporidia," at The Mount Sinai School of Medicine, New York, NY, on October 25, 1991. Final revision received March 1993. From the Department of Ophthalmology, The Mount Sinai Medical Center. Address reprint requests to the author at Box 1183, Mount Sinai Medical Center, One Gustave L. Levy Place, New York, NY 10029.

is available in England but not in the United States. Treatment was prolonged but curative.

By now, many other drugs have been used in efforts to cure ocular acanthamoebal infection. Corticosteroids, in particular, have generated controversy. In their 1991 study of the goals and risks of corticosteroid use in treating different forms of keratitis, Stern and Buttross concluded that these drugs are "relatively contraindicated" for use against *Acanthamoeba* keratitis (9).

Current data suggest that cure is possible if *Acanthamoeba* keratitis is diagnosed early, if appropriate medical treatment is begun promptly, and if that treatment is continued for six to twelve months. Two recently recommended drugs are miconazole and ketoconazole, both antifungal agents that can be used topically and systemically. In 1992, Larkin, Kilvington, and Dart successfully used polyhexamethylene biguanide to treat five of six patients with *Acanthamoeba* keratitis that had proven resistant to conventional antiamebic agents (10).

Risk Factors for *Acanthamoeba* Keratitis

Lens Materials. Infection was not associated with use of the first contact lenses, which were made of polymethylmethacrylate. However, their impermeability to oxygen did cause other problems. All modern contact lenses contain a certain amount of water, which serves as the medium for oxygen flux (11). The water content of soft hydrogel lenses is 50%–75%; that of rigid gas-permeable lenses is usually about 10%. In proportion to their water content, lenses absorb material, including potential pathogens, from cleaning solutions, lens cases, and patients' hands (12, 13). Thus, lens material itself can be a risk factor for acanthamoebal infection.

Lens Cleaning and Disinfection. A soft contact lens is routinely cleaned by placing it in the palm of one's hand and gently rubbing it with a few drops of a surfactant. In addition, soft lenses are usually treated about once a week with enzymes to remove protein deposits. After both of these procedures, the lenses should be disinfected either by heating them in a unit designed for that purpose or soaking them in hydrogen peroxide or other chemical disinfectants. For patients with daily-wear lenses, disinfection is usually an overnight process after which the lenses are ready for use.

Ten years ago, the preservatives in contact-lens solutions were seen as major culprits in causing ocular redness, itching, and lens discomfort, as well as corneal infiltrates. The prevalence of these problems led practitioners to promote the use of unpreserved solutions. Patients were instructed to mix salt tablets and either tap water or distilled water in place of preserved solutions for lens cleaning and storage.

We did not know then that acanthamoebae are ubiquitous in the environment; in particular, we did not know that acanthamoebae are commonly present in the tapwater patients used to make saline solution. The marked increase in acanthamoebal infections during the 1980s certainly was related, in some degree, to patients' switch from using preserved solutions that could disinfect lenses to using unpreserved saline that could not. The use of homemade saline is now actively discouraged.

A related source of lens contamination and, therefore, another risk factor for acanthamoebal infection is many patients' reluctance to take their lenses from a disinfecting solution and directly insert them in the eyes. After all, these solutions are made of chemicals—they are not "natural." As a result, some patients still rinse their lenses with tapwater, again exposing them to acanthamoebae as well as to hosts of other potentially contaminating microorganisms. Other patients, mistaking saline for a disinfectant, use it alone instead of the regimen. Another potential source of pathogens is contaminated eye drops, which patients use to wet their eyes to increase the comfort of lens wear.

Lens Storage Cases. Contact lens care systems are not intended to sterilize lenses; rather, they are disinfection systems designed to reduce the number of organisms that can adhere to contact lenses. However, if these systems are not used in accordance with manufacturers' recommendations, lens disinfection will be inadequate. This will be true, for example, if patients do not use a surfactant before disinfecting their lenses, do not keep the lenses in disinfectant for the prescribed time, or rinse the lenses with tapwater before insertion.

Until recently, ophthalmologists did not consider the possibility that lens cases could be reservoirs for potentially infective organisms. Then Larkin, Kilvington, and Easty (12) examined 102 asymptomatic contact-lens wearers and their lens cases. These patients had good vision, healthy eyes, and unblemished lenses. But cultures of their lens cases showed that nearly half contained significant amounts of bacteria. Seven lens cases contained acanthamoebae.

Donzis et al. (13) studied ten patients whose lens cases were positive for acanthamoebae. All ten cases were positive for gram-negative organisms; in seven, these organisms included *Pseudomonas* species. Five cases also contained gram-positive organisms, particularly bacilli, and six contained fungi. These findings support the conclusion that acanthamoebae do not often occur alone. It is possible that a synergistic or symbiotic relationship exists in which other microorganisms, particularly gram-negative ones, support the growth of acanthamoebae to a density at which they are pathogenic to the eye (13a–14).

Both of these studies made it obvious that many patients' lens-care systems are significantly contaminated. The problem, then, is not just casual exposure of patients' lenses to acanthamoebae. Instead, patients' lenses are frequently, even regularly, exposed to large, diverse, and only partially defined populations of potentially harmful organisms, including, of course, acanthamoebae.

How, then, can systems for the care of contact lenses be made free of acanthamoeba? Even if that question could be satisfactorily answered, there would remain another confounding factor: when patients are instructed to leave their lenses in a disinfecting solution for four hours, some will cut the time to a scant thirty minutes.

Extended Wear. In 1989, Schein et al. (15) found that soft-lens wearers who slept with lenses on their eyes were at approximately ten to fifteen times greater risk of developing ulcerative keratitis than were patients who wore their lenses only during waking hours. In conducting this study, the authors had to control for a wide range of lens-wear patterns. They found, for example, that patients who are instructed to wear their lenses only during the day sometimes wear them to sleep, whereas patients with extended-wear lenses sometimes remove their lenses before going to sleep. Nonetheless, the study results demonstrated that extended wear of contact lenses is the single greatest risk factor for corneal ulcers in soft-lens users. In a survey of New England ophthalmologists, Poggio et al. (16) estimated that the incidence of ulcerative keratitis was only 4.1 per 10,000 daily wearers of soft lenses but 20.9 per 10,000 users of extended-wear soft lenses. Nonetheless, these findings do not wholly explain why the incidence of corneal ulcers, including acanthamoebal ulcers, has increased so markedly in recent years.

Lens Degradation. Repeated and prolonged heating of soft lenses causes them to degrade. In addition, whether they are used for extended wear or are removed, cleaned, and disinfected daily, contact lenses eventually develop deposits. This is unavoidable, for the deposits are, in fact, part of a biofilm. It can be argued that the biofilm is needed, that producing it is the body's reaction to the presence of foreign bodies—in this case, contact lenses. According to this contention, the lenses must be coated with secretions so that the body can recognize the lenses and not react adversely to them. However, the biofilm that coats contact lenses also contains bacteria and contaminating detritus of various kinds, which act as irritants and add to the risk of infection.

Disposable Lenses. Set against the background of all these closely related risk factors, the development of disposable contact lenses seemed to hold great promise. It seemed that these lenses could eliminate all the difficulties relating to lens disinfection, contamination of lens cases, and lens degradation. The patient would wear a pair of new, sterile lenses continually for one week, throw them away, and then start the next week with another pair of lenses. Perhaps there would be no more *Acanthamoeba* keratitis.

This hope seemed to be borne out by early experience. However, it was not long before an association between the wearing of disposable lenses and corneal infections was noted. Among other infective organisms, acanthamoebae were also back (17).

Conclusion

One obvious reason for the increase in *Acanthamoeba* keratitis is the even greater increase in the number of people who wear contact lenses, especially soft lenses. In one study (18) it was found that 80% of the reported cases of this infection occurred among contact-lens wearers. Seventy-five percent of these patients used daily-wear or extended-wear soft hydrogel lenses.

Another reason for the resurgence of *Acanthamoeba* keratitis among contact-lens wearers is indicated by the results of our recent study of 100 patients consecutively fitted with disposable lenses (19). Ninety percent of these patients complied with instructions to wear a pair of lenses for no longer than one to two weeks. To our surprise, however, 60% of the patients were removing and reinserting their lenses at some point within the prescribed period of wear, usually because of dust, dirt, or ocular irritation. Virtually all of these patients reinserted their lenses without disinfecting them; they simply rinsed the lenses, usually with saline or tapwater. It was an old problem—the one that made disposable lenses seem such a boon in the first place.

The final answer is that, in all likelihood, contact-lens wearers will always be at risk of ocular acanthamoebal infection. That conclusion is inherent in the ubiquity of these organisms, the nature of contact-lens wear and care, and the variability of human behavior. All of those factors are emphatic reminders of the importance of educating patients about the risk of infection and the consequent need for rigorous adherence to lens-care regimens. These measures, together with regular, thorough follow-up of all contact-lens patients, remain the first and most essential defense against *Acanthamoeba* keratitis.

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Epidemiology of Infections with Free-Living Amebas and Laboratory Diagnosis of Microsporidiosis

Govinda S. Visvesvara, Ph.D.

Infections Caused by Free-Living Amebas

Free-living amebas occur worldwide. They have been isolated from diverse environmental sources, including fresh and frozen water; vegetables; heating, ventilating, and air conditioning units; cooling towers of electric and nuclear power plants; sewage; medicinal pools; dental treatment units; dialysis units; bacterial, fungal, and mammalian cell cultures; contact lens solutions; corneal scrapings; skin lesions; and the central nervous system of humans (1–3). Among the hundreds of free-living amebas that exist in nature, only those belonging to two genera, *Naegleria* and *Acanthamoeba,* and the newly discovered leptomyxid ameba are known to cause disease in humans (1–4).

Only one species of *Naegleria, N. fowleri,* causes primary amebic meningoencephalitis (PAM), which is an acute, hemorrhagic, necrotizing meningoencephalitis that usually results in death within 5 to 10 days. Amebic trophozoites, but not cysts, are seen in the brain tissue of patients who have died of PAM (**Fig. 1, 2**). Several species of *Acanthamoeba,* on the other hand, are known to cause granulomatous amebic encephalitis (GAE), a chronic disease that may last from one week to several months. Cysts of *Acanthamoeba* are usually seen in the brain tissue of patients with GAE (**Fig. 3**).

As many as 20 species of *Acanthamoeba,* placed in three groups, have been described in the literature. Distinguishing between members of groups using morphologic characteristics is relatively easy, but difficulty arises in identifying members within a group, especially group 2, to the species level on morphologic grounds alone. Hence, nonmorphologic criteria such as antigenicity, isoenzyme profiles, and restriction length polymorphism of genomic DNA are being used increasingly to differentiate the species of *Acanthamoeba* (5–7). Rabbit antisera against 15 of these species have been prepared at the Centers for Disease Control (CDC), and it is possible to identify the species involved, especially in tissue sections, by the judicious use of these antibodies in the indirect immunofluorescence test.

In some instances, amebic trophozoites and cysts in the brain sections of GAE patients have failed to react with any of the antisera, indicating that there are probably species of ameba other than *Acanthamoeba* and *Naegleria* that cause human disease. We at CDC have recently isolated an unusual ameba from the brain sample of an encephalitic baboon from the San Diego Zoo Wild Animal Park (4). Normal procedure for the isolation of small free-living amebas is to inoculate brain, corneal, or environmental samples onto nonnutrient agar plates covered with a layer of bacteria such as *Escherichia coli* or *Enterobacter aerogenes*. We therefore inoculated the samples onto *E. coli*-coated agar plates. We also inoculated the samples onto African green monkey kidney (E6) cells as well as human embryonic lung cells.

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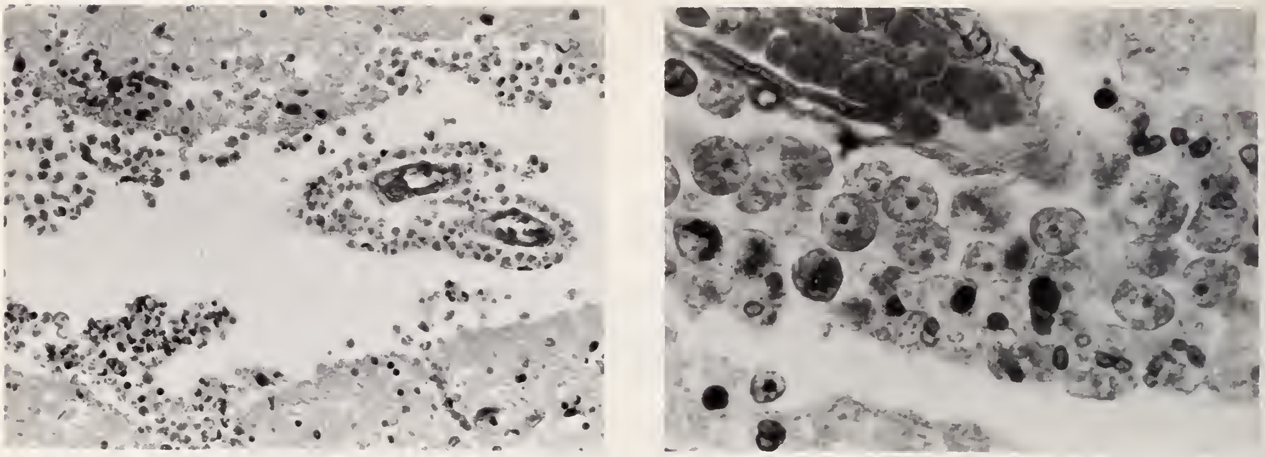

Fig. 1. Brain section of patient with primary amebic meningoencephalitis due to *N. fowleri*. **Left** Note numerous amebic trophozoites and extensive destruction of brain tissue (original magnification ×250). **Right** Higher magnification showing characteristic nuclear morphology of amebas (original magnification ×1,100). Cysts are not seen in sections.

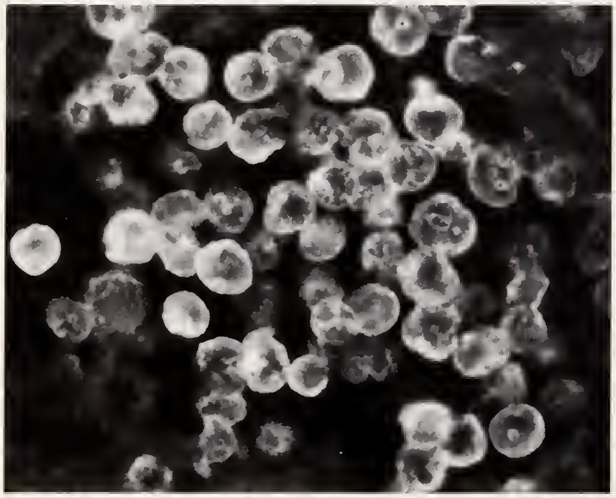

Fig. 2. Immunofluorescence staining of *N. fowleri* amebas in brain section of patient with primary amebic meningoencephalitis (original magnification ×1100). Section was reacted first with monoclonal antibody IV-D1-30, subsequently with goat anti-mouse IgG conjugated with fluorescein isothiocyanate.

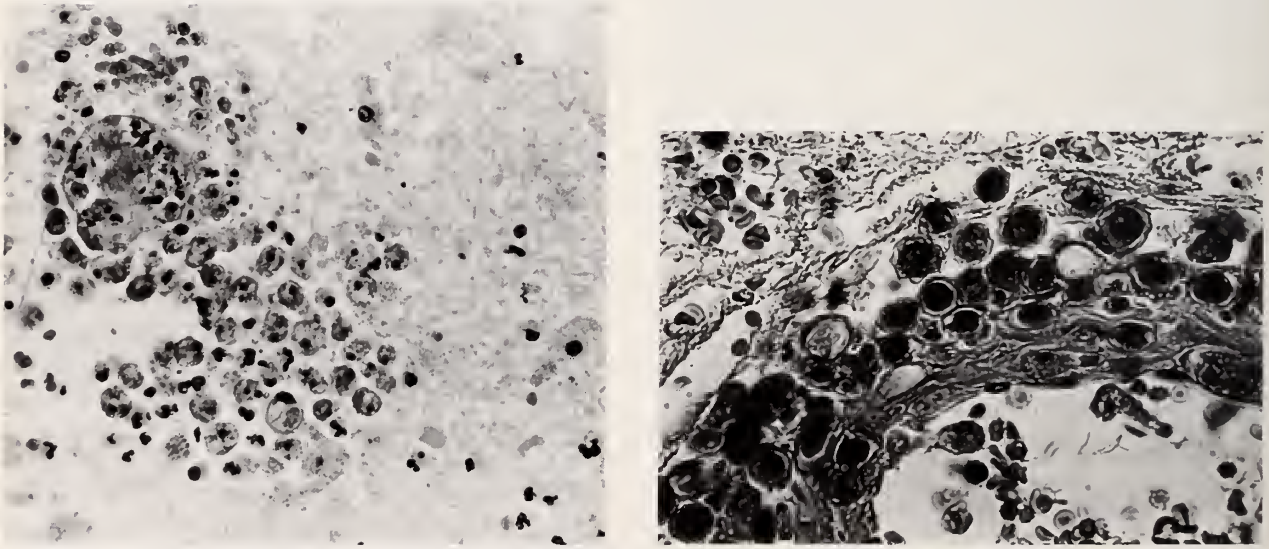

Fig. 3. Brain section of patient with granulomatous amebic encephalitis. **Left** Note numerous *Acanthamoeba* trophozoites (original magnification ×250). **Right** Trophozoites and cysts with characteristic double wall are seen in and around a blood vessel (original magnification ×675).

The agar plates were negative for amebas even after three weeks of incubation. However, in the monkey kidney cell cultures, unusual-looking amebic organisms became noticeable after three weeks of incubation. These structures were morphologically unlike *Acanthamoeba* and *Naegleria* and also did not react with any of the *Acanthamoeba* or *Naegleria* sera, confirming that the ameba in question was neither *Acanthamoeba* nor *Naegleria*. We subsequently identified this agent as leptomyxid ameba, belonging to the order Leptomyxida, previously thought to be a group of innocuous soil organisms (4). We made rabbit antisera against this ameba, and the antisera, when used on the Formalin-fixed brain sections of the baboon, reacted profusely with the ameba in the tissue sections, confirming that this was a new infectious agent that causes central nervous system disease in baboons and possibly in humans. We then tested the anti-leptomyxid sera on tissue sections of several previously unidentified cases of GAE in the indirect immunofluorescence assay. The amebas in these tissue sections all reacted profusely with the anti-leptomyxid serum but not with any of the *Acanthamoeba* or *Naegleria* sera, confirming the notion that this ameba also infects humans.

Lifecycles of Free-Living Amebas

N. fowleri is thermophilic and tolerates temperatures of 40°C–45°C (1). Its lifecycle consists of a trophozoite, a flagellate, and a cyst stage. Under certain circumstances, such as a change in the ionic concentration of the environment, the trophozoite of *N. fowleri* transforms into a nonfeeding flagellate stage. The flagellate will eventually revert back to the trophic stage. The trophozoite measures 10–20 μm and is characterized by the presence of a nucleus with a large central nucleolus. The trophozoite feeds on bacteria such as *E. coli* and rapidly multiplies. It also differentiates into a round, smooth, double-walled cyst during adverse conditions.

Acanthamoeba is slightly larger and has two stages in its life cycle, the trophozoite and the cyst. The trophozoites of *Acanthamoeba* may measure anywhere from 10 to 50 μm, depending on the species. They are characterized by a number of spinelike processes termed acanthopodia that protrude from the surface of the body. *Acanthamoeba* has no flagellate stage. The trophozoite differentiates into a characteristically double-walled cyst during unfavorable conditions. The outer ectocyst is usually wrinkled, whereas the inner endocyst is either stellate, polygonal, oval, or even round.

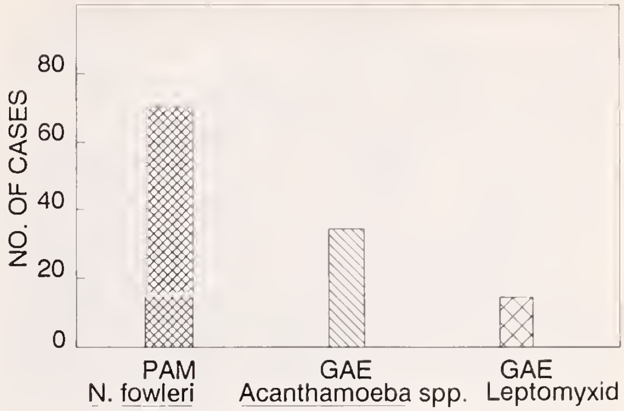

Fig. 4. Reported cases of primary amebic meningoencephalitis (PAM) and granulomatous amebic encephalitis (GAE) in the United States, as of September 1, 1991.

Leptomyxid ameba is larger than *Acanthamoeba* and also possesses a cyst that, at the light microscope level, may be confused with that of *Acanthamoeba*. The trophozoites are irregular and sometimes highly branched and measure from 50 to 60 μm in length. The cysts, which are irregularly round, measure 15–30 μm in diameter and appear to have two walls at the light microscope level. However, at the electron microscope level, three layers of cyst wall may be discerned: an outer wavy wall, a middle structureless layer, and an inner thin endocyst (4). Both the trophozoite and the cyst are uninucleate, but occasionally a few binucleate forms may be seen.

The first reported case of amebic meningoencephalitis caused by free-living amebas was described from Australia by Fowler and Carter in 1965 (7a). At that time it was thought to be due to *Acanthamoeba*, but later the organism was reidentified as *N. fowleri* based on the epidemiologic data, clinical picture, and the small size of the amebas in the tissue sections.

Of the 116 cases of amebic encephalitis recorded at CDC from all over the United States, 59% are due to *N. fowleri*, 29% are due to *Acanthamoeba* spp., and 12% are due to leptomyxid ameba (Fig. 4).

Primary Amebic Meningoencephalitis. The cases of primary amebic meningoencephalitis (PAM) that occurred in 1937 and in the 1950s were diagnosed retrospectively after the first reported case in 1965. Of the 70 cases of PAM, 71% have occurred in males and 29% in females. Although patients have ranged in age from 5 years to 60 years, the majority of cases have occurred in the 15–18 year age group, primarily in healthy young individuals with a history of participating in water-related sports.

The only patient known to have survived this disease in the United States was an 8-year-old girl in 1978 who, along with her parents, had a history of swimming in a hot spring in Southern California. The patient was aggressively treated with amphotericin B, miconazole, and rifampin (8). She is one of the few patients who developed antibodies to *N. fowleri,* with a titer of 4096 in the indirect immunofluorescence test (2). An immunoblot test revealed that the antibody belonged to the IgM class (2). IgM antibody also was present in two other patients who died of this disease despite treatment with the same drugs given to the 8-year-old girl (2). *N. fowleri* amebas isolated from the cerebrospinal fluid of this girl were initially considered to be less virulent organisms; however, mouse pathogenicity tests later revealed this strain to be highly virulent, as it killed mice within 5 to 7 days (unpublished data). Isoenzyme and restriction fragment length polymorphism of the total DNA analysis of this strain both confirmed that this strain is a typical *N. fowleri* (2, 9).

Granulomatous Amebic Encephalitis. *Acanthamoeba* spp. cause *Acanthamoeba* keratitis, *Acanthamoeba* sinusitis, and of course granulomatous amebic encephalitis (GAE) (1–3).

At least 48 cases of GAE have occurred in the United States. Thirty-four of these cases were due to *Acanthamoeba* and the other 14 were due to the leptomyxid ameba. The portal of entry is not clearly known; it could be the upper respiratory tract or skin abscesses. A classic case is that of a 30-year-old Mexican woman who was bitten on the right arm by her daughter (10). The bite area became swollen, red, and indurated, and the inflammation grew for 6 months, after which time she was diagnosed to have tuberculosis and was admitted to a sanatorium in San Francisco. Several punch biopsies of the affected area did not disclose the infectious agent. A few months later she developed neurologic symptoms, and a brain biopsy revealed a large number of amebas. All efforts to culture the organisms were unsuccessful.

As many as 20 cases of *Acanthamoeba* infections have been reported in patients with AIDS. Since the responsible organism has been isolated from only a few cases, specific identification is based on the immunofluorescence reactivities of the amebas in the brain sections. Skin abscesses are a common occurrence in AIDS patients with *Acanthamoeba* infection (11, 12); *Acanthamoeba* organisms have also been isolated from these skin abscesses.

Of the 14 cases of GAE due to the leptomyxid ameba, four occurred in patients with AIDS. Of the 10 cases in non-AIDS patients with the leptomyxid ameba, four occurred in patients 60 years or older, the remaining six in patients under 11 years of age.

***Acanthamoeba* Keratitis.** The first documented case of *Acanthamoeba* keratitis (AK) occurred in 1972 in a Texas farmer who was struck in his eye by a straw while carrying a bale of hay (13). He later developed redness of the eye and was treated for conjunctivitis. A few weeks later he developed unbearable pain, and a corneal biopsy revealed *Acanthamoeba* cysts.

From 1972 through 1984 only 12 cases of keratitis were reported to CDC (14). However, as many as 24 cases were reported in 1985. Examination of patients' records revealed that 20 of the 24 cases were in contact-lens wearers (14). A prospective and retrospective epidemiologic study carried out on 200 AK patients and 600 controls (matched for geographic location, sex, and age) revealed that the risk factors for *Acanthamoeba* keratitis were exposure to contaminated water, corneal trauma, contact lens wear, and the use of unsterile homemade saline solution (15, 16). Seventy-eight percent of patients with AK and 17% of controls used homemade saline as both a predisinfection wetting solution and a postdisinfection soaking agent (15). Many patients also had histories of swimming in lakes, ponds, and pools while wearing contact lenses. The warning issued by the Food and Drug Administration and by the Contact Lens Association of Ophthalmologists on the use of unsterile homemade saline solutions is believed to be responsible for the decrease in the number of *Acanthamoeba* keratitis cases in recent years.

Laboratory Diagnosis of Microsporidia Infections

Microsporidia are typical eukaryotic microorganisms, except for their ribosomes, which are prokaryotic. They are obligate intracellular parasites that occur worldwide and cause disease in almost all major phyla, including protozoans (17). They produce resistant spores and have a unique method of infection. Because of their unique characteristics, they are included in a separate phylum, Microspora. A number of genera in the order Microsporida, including *Encephalitozoon, Nosema, Pleistophora,* and *Enterocytozoon,* are known to cause disease in humans (17, 18). The order Microsporida is divided into two suborders: Pansporoblastina, in which sporogonic development takes place in a sporophorous vesicle, the pansporoblastic membrane (e.g., *Pleistophora*), and Apansporoblastina, in which the sporogonic development occurs in the cytoplasm in the absence of a sporophorous vesicle (e.g., *Encephalitozoon, Nosema, Enterocytozoon*).

Enterocytozoon is the principal cause of diarrhea in patients with AIDS. Some of the enteric problems relate to villus atrophy and fusion, crypt elongation, mild inflammatory infiltrate, depletion of goblet cells, and enterocyte vesiculation and swelling (18). Other genera cause keratitis, myositis, hepatitis, and peritonitis.

Microsporidia are gram-positive. Brown and Bren or Brown and Hops modification of Gram stain can be used with good result. However, electron microscopy is needed to visualize the internal structures. The microsporidian spore measures about 1 × 2 µm and has a complex structure. The spore has a thin electron-dense exospore, a thick electron-lucent endospore, and a thin cell membrane. It has a coiled polar tubule, which is extruded. The infectious sporoplasm travels through the polar tubule and is injected into the host cell. In the transmission electron micrographs the five to seven spherical units that appear on either side of the spore are the cross sections of the coiled polar tubule.

We have recently isolated in culture a microsporidian parasite from the urine of an AIDS patient (**Fig. 5**). It has been continuously grown in monkey kidney cells as well as in human lung fibroblast cell cultures (19). The spores are periodically harvested from the culture flasks by pouring off the supernatant and centrifuging the medium. Fresh medium is then added to the cell culture. The cultures can be maintained and spores harvested for several weeks. After several such harvests, when most of the cells are gone, usually in 8–10 weeks, the medium turns alkaline and spores are usually seen with their polar tubules extruded. To initiate fresh cultures, the sedimented spores are inoculated into a fresh culture flask, or infected cells from the seed flask are scraped and inoculated into fresh cultures.

Spores obtained from cultures can be used as antigens to detect antibodies in the serum of infected patients. Our patient's serum reacted with the antigens from the culture in the indirect immunofluorescence test to a titer of 64. A better diagnostic test—either a serologic or a DNA-based test—is needed so that time-consuming and cost-prohibitive electron microscopy need not be used.

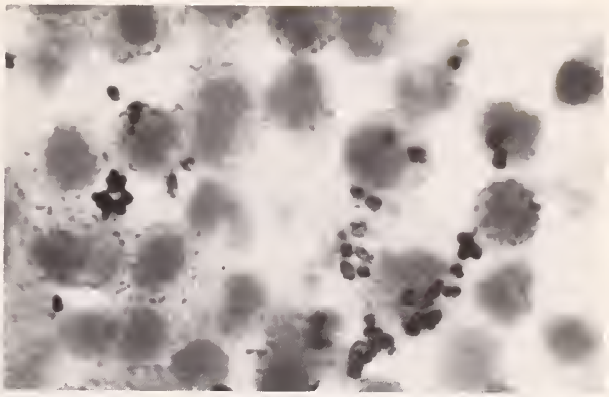

Fig. 5. Microsporidia spores in urine sample stained with Gram stain (original magnification ×1100).

Gram stain or Giemsa stain is currently used to diagnose microsporidia in stool samples (20). One of the biggest drawbacks of this type of staining is that everything on the slide, including bacteria and yeasts, will stain, making it difficult to identify the microsporidia. A differential stain that stains only microsporidia would greatly simplify identification. Dr. Rainer Weber, a visiting scientist at CDC, has recently developed such a differential stain that is basically a modification of trichrome stain (21). The stain uses a tenfold increase in the concentration of Chromotrope R over that of the trichrome stain. Microsporidia spores are stained pinkish red, while bacteria and yeast are stained green. By allowing for differential staining of microsporidia spores in complex specimens such as stool samples, this new stain will facilitate epidemiologic investigations.

Summary

Acanthamoeba, leptomyxid ameba, and microsporidia have recently been recognized as organisms that cause opportunistic infections in patients with HIV and AIDS. As the numbers of patients with HIV and AIDS increase, more cases of amebic encephalitis and microsporidiosis are likely.

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Stroke Prevention in Atrial Fibrillation

Jonathan L. Halperin, M.D., and Elizabeth B. Rothlauf, M.S., R.N.

Abstract

Atrial fibrillation (AF) is a risk factor for ischemic stroke. In randomized trials, AF raised the risk of stroke nearly sixfold, cumulating in a 35% risk over a lifetime. Anticoagulation with warfarin reduces the danger of ischemic stroke, but carries hemorrhagic risks, making this agent unsuitable for treating many patients. Platelet inhibitor therapy with aspirin was highly effective for patients younger than 75 years of age in one study, but the reason for lower efficacy in older individuals is perplexing. These trials support a thrombotic mechanism for most strokes in patients with AF, but leave physicians in a quandary as to selection of optimum prophylaxis. Secondary analysis of patients given placebo identified predictors of thromboembolism, including a history of hypertension, congestive heart failure, and prior stroke or transient ischemic attack, and echocardiographic findings of left ventricular dysfunction or left atrial enlargement. The absence of these risk factors selects a fairly large subgroup of AF patients at comparatively low risk of stroke, for whom the danger and inconvenience of chronic anticoagulation may not be warranted. It is becoming clear that specific clinical and echocardiographic features allow individualized antithrombotic approaches within the broad category of patients with AF, to enhance therapeutic benefit while minimizing hemorrhagic risk.

Effective strategies for prevention of stroke in patients with atrial fibrillation require first that the problem of cardiogenic embolism be placed in perspective. The vast majority of clinical stroke events—fully 85%—are related to ischemic infarction of the brain; the rest are due to hemorrhage. Of these ischemic strokes, most are due to diseases of the extracranial or intracranial arteries; no more than 15% can be specifically traced to thromboembolism from the cardiac valves or chambers. At least half the cases of suspected cardiogenic embolism occur in patients with a history of atrial fibrillation, but some have rheumatic heart disease, prosthetic valves, hypertension, or left ventricular dysfunction, which are independently associated with stroke (**Fig. 1**) (1). About one in four embolic episodes is related to ventricular thrombi, as occur in patients with acute myocardial infarction, particularly within the first 10 days of large anteroapical infarcts, or in patients with chronic cardiomyopathy (2). Patients with left ventricular aneurysm formation are at lower risk of embolism even though mural thrombus is frequently present, perhaps because stasis prevails in the aneurysmal sac so that dynamic circulatory forces do not mobilize the thrombotic mass (3).

Particular thromboembolic risk is associated with nonvalvular (nonrheumatic) atrial fibrillation, which raises the chance of stroke about sixfold, to more than 5% per year. This risk was first recognized in epidemiologic projects such as the Framingham Heart Study, which found an even stronger association of nonvalvular atrial fibrillation with stroke among elderly patients (4). Many of the ischemic strokes that occur in patients with atrial fibrillation may not have a cardioembolic mechanism, because coexisting hypertension or atherosclerosis contributes to ce-

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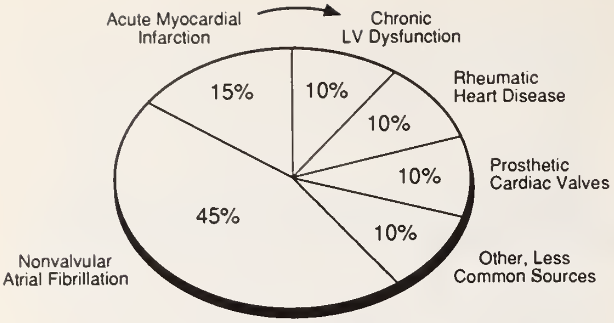

Fig. 1. Nonvalvular atrial fibrillation is associated with nearly half the cases of cardiogenic embolism; valvular heart disease, acute and chronic left ventricular dysfunction, and other disorders account for the remainder (10).

rebrovascular pathology, and it is seldom certain whether a given clinical event was caused by embolism of thrombotic material originating in the fibrillating left atrium. Carotid atherosclerotic disease may account for some cases, but Weinberger et al., found a potential carotid source for cerebral ischemic symptoms in fewer than a third of patients with nonvalvular atrial fibrillation examined by ultrasound imaging of the extracranial arteries (5). Until the results of randomized trials became available, prophylactic antithrombotic therapy was based entirely on a theoretical concept: atrial fibrillation creates a situation of stasis within the left atrium, particularly the atrial appendage, leading to formation of fibrin and thrombin. Administration of an anticoagulant such as warfarin has been considered appropriate in patients at high risk, though risk groups were poorly defined. Platelet activation has been thought less important in the pathogenesis of cardiogenic embolism than in atherosclerotic disease, so a role for platelet inhibitor medication such as aspirin was until quite recently entirely speculative (6).

Refining Definitions of Risk Groups. Population-based data indicate that within the broad category of patients with atrial fibrillation, not all are at equal risk of stroke. Those at high risk (event rates over 6% per year) are patients with rheumatic mitral stenosis, previous cerebral ischemia or systemic embolism, prosthetic heart valve (particularly mechanical prosthesis in the mitral position), or dilated cardiomyopathy (7). On the other end of the spectrum are patients with "lone" atrial fibrillation, younger individuals without organic cardiopulmonary disease in whom atrial fibrillation is often paroxysmal or intermittent (8). A series of 97 such patients under age 60 years followed over a period of 17 years had an incidence of ischemic stroke well below 1% per year, comparable to people in sinus rhythm (9).

Between these poles lies the majority of patients with nonvalvular atrial fibrillation, who were, until recently, at uncertain or intermediate risk. Here, too, lies a great deal of medical lore: false or unverified teachings based on notions of pathogenesis that have not been evaluated in properly conducted randomized trials. These notions are the source of some of the concern about thromboembolism surrounding restoration of sinus rhythm by chemical or electrical cardioversion. Although paroxysmal atrial fibrillation necessarily entails frequent spontaneous conversion to sinus rhythm, there is no greater risk of stroke than with constant fibrillation (10). Similarly, while the Framingham Study suggested an increased risk of stroke during the period immediately after detection of atrial fibrillation, in recent studies the risk appears cumulative, events occurring at a more or less constant rate over years (11). The diagnosis of "silent" stroke, based on areas of infarction on computerized-tomographic or magnetic resonance images of the brain, may also identify a group of patients with atrial fibrillation at greater risk of clinical stroke; the same may prove true when there is carotid atherosclerotic disease, but the importance of these additional risk factors has yet to be verified (12).

To the cardiologist, the most important issue is the underlying etiology of atrial fibrillation, best defined by clinical history and echocardiography. Mitral regurgitation appears to reduce the risk of stroke by minimizing stasis and thrombogenicity within the left atrium. Only recently has enlargement of the left atrium been validated as a predictor of stroke risk in patients with nonvalvular atrial fibrillation, just as it is in cases of valvular heart disease. Even more important, the finding of impaired left ventricular function has been recognized as a powerful marker of thromboembolic risk (13). Left atrial thrombi, only rarely identified by transthoracic echocardiography, may not be directly associated with an increased risk of stroke, since the clinical problem is not one of thrombus formation, but rather of embolic migration to the vessels supplying the brain (14).

Who Are the Candidates for Anticoagulation Therapy? Whatever our notions of pathogenesis, nonvalvular atrial fibrillation carries a risk of stroke at least six times that of patients in sinus rhythm. The scope of the problem is considerable: over a million North Americans with a 35% lifetime risk of stroke in the absence of antithrombotic therapy. These neurologic events are often devastating, stealing language and movement and dehumanizing victims. The toll in human terms is inestimable, but the cost of acute and convalescent care for stroke victims comes to nearly a billion dollars a year in the United States alone. Although potent antithrombotic medication has been available for decades, it has until recently been unclear which patients should be exposed to the hemorrhagic risks of anticoagulation, particularly as no alternative treatment had proven prophylactic value (15).

In 1987, investigators sponsored by the National Institute of Neurological Disorders and Stroke—70 cardiologists, neurologists, and research nurses from 15 medical centers—began working together to evaluate antithrombotic therapy for patients with nonvalvular atrial fibrillation. The initial Stroke Prevention in Atrial Fibrillation (SPAF) study was a randomized clinical trial comparing warfarin, aspirin, and placebo in patients with electrocardiographically documented atrial fibrillation (sustained or intermittent) without mitral stenosis or prosthetic heart valves, who did not have either a proven medical need for or contraindication to antithrombotic therapy.

Patients considered candidates for anticoagulation entered group I of this two-part trial and were randomly assigned to treatment with warfarin, aspirin, or placebo. Those with contraindications to anticoagulation or an unwillingness to accept the risk and inconvenience of prothrombin time monitoring necessary with this form of therapy entered a parallel trial, group II, in which treatment consisted of either aspirin or placebo (**Fig. 2**) (16). It was projected that 1644 patients would be required to compare aspirin, 325 mg daily in enteric-coated form, and warfarin, dose adjusted to raise prothrombin time to 1.3–1.8 times control, with placebo for reduction in the primary end-point events—ischemic stroke and systemic embolism. Only aspirin and placebo were given in double-blind fashion. To compensate for the unblindedness of warfarin treatment, a method of blinded-event verification was employed.

Aspirin or Warfarin? After the trial had progressed for little more than a year, a safety-monitoring committee recommended stopping administration of placebo because of the clear superiority of active antithrombotic medication for stroke prevention (**Fig. 3**). A dramatic reduction (by more than 80%) in the incidence of ischemic stroke and systemic embolism was evident in group I (warfarin-eligible) patients given either aspirin or warfarin. It became clear that patients with nonvalvular atrial fibrillation should be given some form of antithrombotic medication, but the study had insufficient statistical power to determine which type (aspirin or warfarin) was more effective. Given the small number of ischemic events in patients taking these medications, even had all strokes occurred in patients assigned to receive one agent or the other, the less effective therapy would still have been 61% better than no treatment (17).

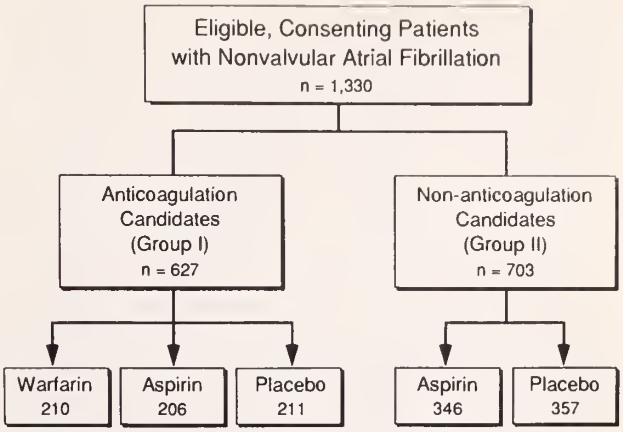
Eligible, Consenting Patients
with Nonvalvular Atrial Fibrillation
n = 1,330
Anticoagulation Candidates (Group I)
n = 627
Non-anticoagulation Candidates (Group II)
n = 703
Warfarin 210
Aspirin 206
Placebo 211
Aspirin 346
Placebo 357

Fig. 2. Design of the Stroke Prevention in Atrial Fibrillation study. Eligible consenting patients were categorized as warfarin eligible (group I) or warfarin ineligible (group II) (16).

The effect of aspirin was not uniform, as patients in group II did not show the same benefit of the platelet inhibitor as those in group I. This differential effectiveness of aspirin forced the investigators to examine reasons patients entered group II rather than group I. The most frequent reason was simply the refusal of otherwise eligible patients to accept potential assignment to warfarin therapy, and these patients responded to

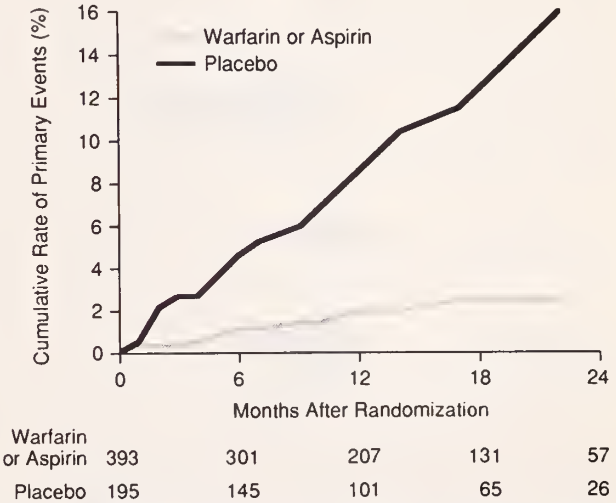

Fig. 3. Rates of stroke and systemic embolism (primary events) in patients given active therapy (warfarin or aspirin) or placebo in group I of the Stroke Prevention in Atrial Fibrillation (SPAF) study (17). Number of patients appears at the bottom.

	n	stroke risk reduction %	bleeding rate %/yr
AFASAK	1007	53	0.5
SPAF	1330	67	1.5
BAATAF	420	86	0.8
CAFA	383	35	2.1
SPINAF	538	74	1.1
Aggregate		**69**	**1.2**

Fig. 4. Five antithrombotic therapy trials for patients with nonvalvular atrial fibrillation: Copenhagen Atrial Fibrillation-Aspirin-Anticoagulation (AFASAK) trial, Stroke Prevention in Atrial Fibrillation (SPAF), Boston Area Anticoagulation Trial for Atrial Fibrillation (BAATAF), Canadian Atrial Fibrillation Anticoagulation (CAFA), Veterans Administration Cooperative Stroke Prevention in Nonvalvular Atrial Fibrillation (SPINAF). The percent risk reduction and bleeding rates for patients anticoagulated in each trial are presented (18–21, 24).

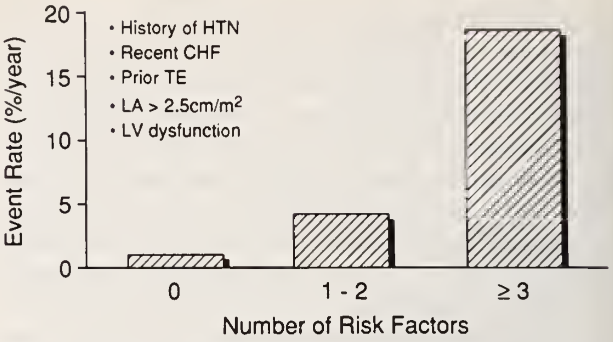

Fig. 5. Predictors of thromboembolism in the Stroke Prevention in Atrial Fibrillation (SPAF) trial. One or more risk factors was associated with an increased event rate for patients with nonvalvular atrial fibrillation given placebo rather than aspirin or warfarin. Nearly half the enrollees with none of these risk factors had a low event rate even without antithrombotic therapy (13, 22). HTN, hypertension; CHF, congestive heart failure; TE, thromboembolism; LA, left atrium; LV, left ventricle.

aspirin as favorably as those in group I. The most frequent clinical reason for exclusion from the anticoagulant group was age over 75 years, in part because of an initial protocol stimulation that these older patients be assigned only to aspirin or placebo. When the effect of aspirin was examined on the basis of patient age, effective prophylactic value was confirmed for those under 75 years old, but in the older group, event rates were identical whether patients took aspirin or placebo. Although the effectiveness of warfarin for prevention of ischemic stroke was not linked to age, bleeding complications, particularly, may have been age-related. Overall, hemorrhagic events sufficiently severe to require hospitalization, transfusion, or surgery occurred in nearly 2% of patients treated with warfarin, even when prothrombin time values were frequently monitored (18).

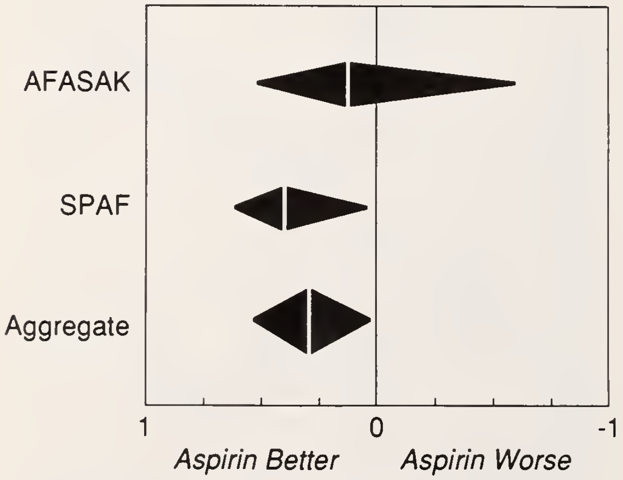

Fig. 6. Event rates of patients assigned to aspirin in the Atrial Fibrillation-Aspirin-Anticoagulation (AFASAK) trial and the Stroke Prevention in Atrial Fibrillation (SPAF) trial (18, 19). Meta-analysis reveals an overall benefit of aspirin for stroke prophylaxis.

Over the last three years, the results of five randomized trials of antithrombotic therapy involving patients with nonvalvular atrial fibrillation have become available. These include the Copenhagen Atrial Fibrillation-Aspirin-Anticoagulation (AFASAK) trial, which found warfarin but not aspirin (75 mg daily) significantly effective; the average age of the patients was 75 years (19). In the Boston Area Anticoagulation Trial for Atrial Fibrillation (BAATAF), patients were followed longer than in the other trials; warfarin was effective even at a low intensity, but the control group did not include a placebo, and nearly half the patients acknowledged taking aspirin. This may be one reason the event rate was lower than in other series (20). The Canadian Atrial Fibrillation Anticoagulation (CAFA) study was terminated before statistically significant results were obtained, because it was not deemed acceptable to continue placebo in view of the results in other trials (21). Data from the Veterans Administration cooperative Stroke Prevention in Nonvalvular Atrial Fibrillation (SPINAF) trial have been reported only in preliminary form; warfarin proved effective for stroke prevention in patients with nonvalvular atrial fibrillation, but aspirin was not tested (21a).

Taken in aggregate, these studies convincingly demonstrate that patients with atrial fibrillation who receive no active antithrombotic medication have a sixfold greater risk of ischemic stroke than comparable patients in sinus rhythm, amplifying the conclusions drawn from epidemiologic studies. The rate of disabling strokes is at least 2.5% per year, and if one includes transient ischemic attacks and clinically silent stroke events detected by cerebral imaging, the risk is even greater. Warfarin reduces the risk of stroke by nearly 70%. Bleeding during anticoagulant therapy occurred at a rate only slightly over 1% annually, but participants in these trials were carefully selected and followed closely according to strict research protocols (**Fig. 4**). It seems likely that broad application in general clinical practice, particularly when elderly patients are included, might be associated with substantially higher bleeding risk.

Identifying Safe Anticoagulation Candidates at High Risk of Stroke. To clinicians, the data are already sufficient to clarify that warfarin is effective medicine for patients with atrial fibrillation. The question has now become not whether this form of treatment works, but rather which patients need it. The SPAF investigators examined entry characteristics of 568 patients assigned to the placebo arms using a stepwise method of secondary analysis. Overall, three features available from the clinical history were associated with statistically significant increased relative risk of stroke during follow-up: (a) a history of hypertension, (b) prior thromboembolism (stroke or transient ischemic attack more than two years before enrollment), or (c) congestive heart failure within three months of entry. Transthoracic M-mode and two-dimensional echocardiographic findings were also analyzed, and the finding of left ventricular dysfunction was the most important echocardiographic predictor of stroke risk. Left atrial enlargement beyond 2.5 cm/m^2 was also correlated with increased stroke risk (**Fig. 5**) (22).

Taken together, these clinical and echocardiographic parameters were not only useful in identifying patients with high risk of stroke, but 42% of the population could be identified as at low risk—too low to justify the hemorrhagic risks, nuisance, and expense of chronic anticoagulant therapy. This is particularly true when one considers that a safer alternative to anticoagulation exists. A meta-analysis of the SPAF and Copenhagen AFASAK studies seems to show that aspirin is effective for stroke prevention in atrial fibrillation, at least for some patients (**Fig. 6**).

There remains the clinical dilemma: which type of therapy to offer specific patients. For now, a logical approach would be to administer warfarin in patients considered safe anticoagulation candidates, particularly when the risk of thromboembolism is high based on a clinical history of hypertension, thromboembolism, or congestive heart failure or when left ventricular dysfunction or enlargement of the left atrium is evident echocardiographically. It is also clear that relatively low intensity anticoagulation may be sufficient. Safe anticoagulation requires use of the International Normalized Ratio of prothrombin suppression to compensate for variable sensitivities of thromboplastin reagents used for prothrombin time determinations (23).

Patients may be appropriately treated with aspirin when clinical and echocardiographic features suggest a low thromboembolic risk or an increased risk of bleeding during warfarin anticoagulation. The decision might also be based on predicted aspirin effectiveness, though this requires a good deal of pathophysiologic speculation. Fortunately, trials are currently in progress comparing warfarin and aspirin in patients with atrial fibrillation, including the SPAF-II study, which is examining this issue in parallel populations older and younger than 75 years of age.

The future may offer even better alternatives, perhaps combining the best of both worlds by administering low doses of aspirin with very low intensity anticoagulation, to enhance therapeutic benefits while minimizing hemorrhagic risks.

At this point, one overriding principle is clear: virtually all patients with nonvalvular atrial fibrillation should be given warfarin or aspirin for stroke prevention. Atrial fibrillation is associated with up to 100,000 strokes annually in the United States at a cost approaching $1 billion each year. The simple prescription of an aspirin could prevent 150 strokes a day.

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Grand Rounds

Frontiers in the Treatment of Ischemic Stroke

Stanley Tuhrim, M.D.

Abstract

Advances in the understanding of the pathophysiology of ischemic neuronal death have led to the development of new approaches to treating acute stroke. Concurrently technologic advances have permitted application of older approaches in a more sophisticated manner. These advances herald an era in which rapid, precise evaluation and treatment of the patient with acute stroke may dramatically alter prognosis. This article reviews some of these advances.

In the past decade, many new insights into stroke treatment have altered the approach to patients with cerebrovascular disease. An evolving understanding of the pathophysiology of the acute ischemic process has produced new avenues for possible intervention based on knowledge of the intracellular mechanisms underlying ischemic neuronal death. This article will review some of the exciting new approaches to acute ischemic stroke therapy.

The Ischemic Penumbra

Experimental models of cerebral ischemia have demonstrated a continuum of changes when cerebral blood flow (CBF) is reduced below the normal resting rate of 50–55 mL/100 g/min, leading first to neuronal dysfunction and then to cell death.

Normal cerebral perfusion pressure maintains membrane potentials, allows appropriate processing of neurotransmitters, and supports normal cellular architecture. Below 30 mL/100 g/min there is an increase in extracellular hydrogen ion concentration. CBF below 20 mL/100 g/min produces an increase in extracellular potassium ion concentration and in intracellular calcium ion concentration that results in a loss of electroencephalographic activity and evoked potentials. This indicates dysfunction, but not necessarily irreversible cell damage. The potential for recovery exists if blood flow is restored to adequate levels. CBF below 10–15 mL/100 g/min results in membrane depolarization and cell death.

The length of time neurons can be deprived of adequate blood flow and remain viable is unclear, but dysfunctional cells may exist in this state for hours and return to normal if blood flow is restored. In acute ischemic stroke, cerebral tissue immediately adjacent to an infarcted area may be deprived of sufficient blood flow to function, yet remain viable. This region, which may be extensive compared to the irreversibly damaged area, has been termed the ischemic penumbra (1). Its existence provides a window of opportunity for remedial intervention larger than the few minutes that was assumed when dysfunction was equated with cell death, but also indicates that potential for exacerbating injury if the patient is treated inappropriately.

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TABLE
Cellular Therapies

Mechanism	Example
Preventing calcium ion flux	Calcium channel blockade
Moderating excitatory neurotoxins	NMDA receptor blockade
Reducing cerebral oxygen demands	Hypothermia, barbiturates
Neutralizing free radicals	Vitamin E, superoxide dismutase
Protecting cell membranes	GMI ganglioside
Reducing lactate production	Lowering blood sugar

Hypertension in Acute Ischemic Stroke

Controlling hypertension is a major component of stroke prevention, but most strokes occur in patients with a history of hypertension. Treating elevated blood pressure in the setting of acute stroke can exacerbate the ischemic injury. In the normal individual, cerebral autoregulation maintains CBF near 55 mL/100 g/min at mean arterial pressures between 55 and 125 mm Hg. However, chronically hypertensive patients may maintain autoregulation only in a higher range, perhaps only beginning at the upper limit of the range in normal persons (2). Below this level, CBF would be dependent on systemic arterial pressure, so that decreasing the systemic pressure to the "normal" range could decrease CBF below levels critical to maintaining adequate perfusion, especially of the ischemic penumbra. This situation may be even more dangerous in the setting of acute stroke because autoregulation is impaired in areas of ischemic brain, increasing the likelihood that lowering systemic pressure will further compromise marginally perfused tissue (3). Blood pressure regulation in acute ischemic stroke is a pervasive issue, since 84% of stroke patients are hypertensive on hospital admission (although by poststroke day 10 only 33% remain hypertensive without antihypertensive therapy) (4). An understanding of the concept of the ischemic penumbra and cerebral autoregulation indicates the prudence of not lowering blood pressure in the setting of acute ischemic stroke unless other vital organs (e.g., heart, kidney) are compromised or blood pressure rises to levels associated with hypertensive encephalopathy (i.e., diastolic pressures greater than 130–140 mm Hg) where further neurologic damage, presumably from cerebral edema, may ensue.

Cellular Therapies

Potential therapies for acute ischemic stroke can be broadly categorized into one of two approaches. Cellular therapies, based on an as yet imperfect understanding of the biochemical consequences of ischemia, attempt to intervene at the neuronal level. Some of these are listed in the Table. Reperfusion therapies aimed at restoring blood flow to the ischemic region are discussed below.

Early attempts to treat the biochemical consequences of ischemia tried to reduce metabolic demand. However, anesthetics, barbiturates, and hypothermia, although seemingly effective in experimental models of ischemia, have not proven efficacious in acute ischemic stroke in humans. Attention has shifted to the role of calcium homeostasis and its disregulation in ischemia. Normally, extracellular free calcium concentration are 10^4 higher than intraneuronal levels. Maintenance of this gradient is crucial to the function of the neuron. Intracellular calcium homeostasis is mediated via two types of calcium channels, voltage-dependent channels (VDC) and receptor on neurotransmitter-operated channels (ROC), and may be affected by nonspecific membrane leakage as well.

Voltage-Dependent Calcium Channels. Cell membrane depolarization activates VDC, allowing calcium ion influx. Three types of VDC, transient, intermediate, and long-lasting (or L-type) channels, have been identified. The L-type channel is the most important mediator of calcium ion influx in ischemia and has been the target for pharmacologic manipulation with at least four distinct classes of calcium antagonists, of which the dihydropyridines, including nimodipine and nicardipine, have been most extensively tested. By binding to specific recognition sites, these agents produce a conformational change that results in inactivation of the L-type channel. In part because they are lipophilic and can cross the blood-brain barrier, these agents are relatively "cerebroselective," exerting their greatest effect in the central nervous system, increasing cerebral blood flow by dilating cerebral vessels via their effect on smooth muscle cells and blocking calcium influx into ischemic neurons.

Nimodipine has been studied in at least seven clinical trials and has consistently been shown to mitigate the ischemic neuronal damage secondary to vasospasm following subarachnoid hemorrhage. However, no effect of nimodipine on angiographically demonstrable vasospasm has been found (5).

In effect, treating patients with subarachnoid hemorrhage with nimodipine is pretreating patients at high risk for cerebral infarction before they suffer an ischemic insult. The results have not been as encouraging when nimodipine has been tested in ischemic stroke patients treated up to 48 hr after stroke onset. An initial study demonstrated significantly reduced mortality at one month in ischemic stroke patients treated with oral nimodipine, 120 mg daily, compared with placebo (6), but three subsequent studies failed to confirm this (7). If only patients treated within 12 hr of onset are considered, however, a beneficial effect can be noted. Therefore, a trial in which patients are treated within 12 hr of onset has been suggested.

Receptor or Neurotransmitter-Operated Calcium Channels. The primary ROC for calcium entry is the *N*-methyl D-aspartate (NMDA) receptor channel. Glutamate binds directly to this receptor, allowing calcium influx. Drugs can block this activity, by competing with glutamate for its binding site or by binding at another receptor on the channel, termed the phencyclidine (PCP) receptor, and directly preventing calcium influx. This second, noncompetitive, inhibition with drugs such as MK801 or dextromethorphan has been shown to reduce infarction size in laboratory models (8). However, because of undesirable side effects, including hallucinations and respiratory depression, associated with these agents, further refinement may be required before this approach proves useful. Other means of influencing calcium ion homeostasis, including intracellular calcium chelation and moderating non-NMDA-mediated receptor-operated channels, are under laboratory investigation.

Free radicals containing impaired electrons can be generated in areas of incomplete ischemia such as the ischemic penumbra. They may cause further injury to cells via peroxidation, particularly during reperfusion of an ischemic area. Drugs that interfere with lipid peroxidation, such as superoxide dismutase, have been shown to reduce infarct size in laboratory models (9). In particular 21-aminosteroids, a class of compounds derived from methylprednisolone, but lacking both glucocorticoid and mineralocorticoid effects, are currently under study in human clinical trials for both head trauma and ischemic stroke. Another antioxidant, vitamin E, could also prove useful in neutralizing the effects of free radicals.

Reperfusion Therapies

Arterial occlusion by thrombosis is the proximate cause of brain infarction. Clot lysis or prevention of clot propagation so as to restore blood flow or preserve collateral flow would seem an obvious intervention strategy, yet no such therapy has been proven effective. Several approaches are, however, currently under investigation.

For 40 years the antithrombotic therapy most widely favored has been anticoagulation with heparin, but its use remains controversial. Results of studies performed to date have been conflicting, some early studies suggesting a benefit in progressing stroke (10), but more recent ones failing to show a benefit (11). However, all studies to date have had significant methodologic limitations, such as lack of randomization or insufficient sample size. A greater consensus exists regarding the usefulness of heparin in preventing recurrent stroke in patients suffering a cardioembolic stroke. A randomized trial of anticoagulation in patients with acute stroke presumed to be cardioembolic in origin was terminated after only 45 patients had been entered, because anticoagulation was thought beneficial, although even this conclusion has been questioned (12).

Low-molecular-weight heparinoids have been studied as a potentially safer alternative to heparin because they have a negligible effect on platelets while maintaining potent antithrombotic effects and are therefore less likely to produce bleeding complications or thrombocytopenia. A semisynthetic, low-molecular-weight heparinoid, ORG 10172, is currently under study in a double-blind, placebo-controlled trial in the prevention of ischemic stroke progression. This well-designed study should avoid the methodologic limitations of previous ones. In preliminary studies, this compound has proven relatively safe when given to acute stroke patients, although 2 of a total of 83 patients treated in two studies did suffer fatal hemorrhagic conversions of large infarctions (13).

Because of recent successes in treating myocardial infarction, there is renewed interest in thrombolytic therapy for acute stroke. The endogenous thrombolytic system provides a counterbalance to clotting mechanisms in order to maintain homoeostasis. Formation of thrombus activates the thrombolytic system, allowing for restriction and lysis of intravascular thrombosis. Enhancing this response promotes recanalization of vessels occluded by thrombus. Tissue plasminogen activator (tPA) produced by vascular endothelial cells and urokinase are endogenous activators of the thrombolytic system; streptokinase is an exogenous substance that can be administered with similar effect.

Initial studies of thrombolysis following ischemic stroke, performed 30 years ago, were discouraging, leading investigators to temporarily abandon this approach. However, these early attempts had significant methodological shortcomings, including the lack of availability of computed-tomography (CT) scanning, limiting both the initial distinction between intracerebral hemorrhage and ischemic stroke and the early detection of iatrogenic intracerebral hemorrhage. Patients were sometimes treated days after onset, when restoration of blood flow would be of limited value. More recently, with the availability of CT scanning, magnetic resonance imaging, and superselective cerebral angiography allowing delivery of thrombolytic agents directly to the thrombosed vessel, several reports have indicated encouraging results (14, 15). Recanalization of the affected vessel is usually achieved, but since none of the intra-arterial studies of urokinase or streptokinase have been randomized or blinded, a true test of efficacy has yet to be performed.

Studies of intravenous thrombolytic therapy have generally employed a form of tPA. Two randomized trials of efficacy are currently underway, but earlier studies intended to test safety and determine appropriate dosing have demonstrated that arterial recanalization can be achieved. The rate of hemorrhagic complications reported has varied widely from 4% to 50%, with a mortality rate approaching 50% (16).

Although definitive efficacy is lacking, acute reperfusion therapies show great promise and are intuitively attractive because they attack the proximate cause of ischemic stroke. Many questions remain regarding this approach relating to timing, method (intravenous or intra-arterial), dose, agent, and use of concomitant anticoagulation or antiplatelet therapy. Nevertheless, restoration of adequate blood flow appears key to salvaging ischemic brain.

Agents that act at the cellular level have been demonstrated to protect the ischemic brain from irreversible damage, partially mitigating the effects of inadequate blood flow. As-yet-untried combinations of these agents may prove far more effective than isolated approaches. Potentially, these agents, alone or in combination, may be able to forstall or limit cell death until adequate blood flow is restored. Ultimately the combination of cellular and reperfusion therapies may dramatically alter the prognosis of acute ischemic stroke.

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Urologic Aspects of Prevention of End-Stage Renal Disease in Spinal Cord Injury

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YEARS AGO the primary cause of death in persons with spinal cord injury was end-stage renal failure. The last 10 years have witnessed a revolution in the way we have come to understand the physiology of the bladder and how to best manage its functions after spinal cord damage. As a result, end-stage renal failure is no longer the leading cause of death, which is now cardiopulmonary disorders. A 25-year-old patient with spinal cord injury has a life expectancy of 50–60 years—dramatic testimony to the importance of proper bladder management and to the inapplicability of earlier modalities of urologic treatment; it is no longer acceptable to simply insert a Foley catheter or a suprapubic tube and assume that the urinary tract has been adequately managed.

In the management of the neurogenic bladder in such patients, the primary objective is to prevent renal damage and subsequent failure. Continence and the prevention of pressure sores are still important, but not difficult to manage.

Effects of Spinal Cord Injury on the Bladder. In spinal cord injury, there is an interruption of neurons between the pontine micturition center, which coordinates the activities of the bladder and external sphincter, and the pudendal and pelvic nerve nuclei in the sacral cord. The bladder will therefore contract spontaneously with simultaneous contraction of the external sphincter (dyssynergia), an undesirable event of grave potential harm in the upper urinary tract.

In addition, the hypogastric nerve arising from T-11 through L-1 exerts an accommodating effect, maintaining low pressure intravesically during the filling phase. This effect is dampened during the voiding phase, when the pressure increases under the influence of the pelvic nerve.

Receptors and Drug Choices. The alpha agonist receptors are primarily at the bladder neck and the urethra. If the patient is treated with an alpha agonist like pseudoephedrine, for example, the bladder neck and urethra tone will increase. In fact, this kind of medication is sometimes used in women with incontinence associated with coughing or sneezing. Alpha blockers are used to produce the opposite effect—to relax muscle tone. Minipress (Prazosin) will relax the bladder neck area to some extent but will not affect the external sphincter, which is unaffected by any oral agent.

Beta agonists, which act primarily on the dome of the bladder for relaxation, are not used clinically to any extent. Instead, anticholinergic drugs are used to act on the cholinergic receptors of the pelvic nerve. Oxybutynin (Ditropan) and propantheline bromide (Probanthine) are the most commonly used anticholinergic medications. They block the parasympathetic influence on the detrusor muscle so that its contractility is impaired, sometimes to the point of paralysis. A cholinergic agonist, such as bethanechol (Urecholine), will, conversely, increase the tone of the bladder.

Clinical Course of Bladder Effects. The initial effect is a period of inactivity (areflexia) lasting from 1 to 24 weeks. Generally within 4 to 6

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weeks the bladder gradually resumes automatic contractions but without the influence of the cortex or the pontine micturition center. There is a gradual return of contractions and the establishment of a permanent contractile pattern as some of the edema resolves in the cord after the injury. There may be a resolution of the dyssynergia, and a more specific pattern of bladder pressures during the filling and voiding phases will be established. The permanent pattern of injuries low on the spinal cord, at the conus medullaris or the cauda equina, is usually areflexia.

Injuries above the T-6 level have an impact on the control of sympathetic outflow. This may result in autonomic dysreflexia, an uncontrolled discharge from the sympathetic portion of the thoracolumbar cord. It is triggered by noxious stimuli arising primarily in the sacral cord dermatomes. One of the most common stimuli is a full bladder. Autonomic dysreflexia can lead to cerebral hemorrhage, since systolic blood pressure can rise rapidly to more than 200 mm Hg.

Dyssynergia often results in high-pressure voiding, with consequent hydronephrosis and stone formation. The post void residual (how much urine is left in the bladder after voiding) is not as important as the pressure required for the bladder to expel urine. High pressure in spinal cord injury occurs if the sphincter does not open at the time of the voiding phase.

In addition to high-pressure voiding, one may encounter high-pressure filling, which can be just as dangerous to renal function if low-pressure accommodation is impaired by injury to the hypogastric nerve or to the cord at the T-11 to L-1 levels.

A urodynamic study is the only way to determine whether there is high pressure in the bladder. A cystometrogram with fluid contrast, and simultaneous urethral or sphincter pressure measured during the filling and voiding stages, is ideal. A 10 French triple-lumen catheter is usually used to allow measurements of both the bladder and the urethral pressure. Fluoroscopy is needed to monitor the appearance of the bladder and the bladder neck and to ascertain the presence or absence of reflux.

Management. When the bladder becomes severely trabeculated (often attaining the appearance of a Christmas tree), continuing high pressure will lead to deterioration of the upper tracts and eventual end-stage renal failure. There are two choices in this clinical picture. Intermittent catheterization can be performed often enough to prevent the high pressure from occurring. However, if the frequency of the pressure elevations noted in the urodynamic tracing indicates that catheterization would have to be performed more often than every three hours, this treatment becomes impractical. The alternative is to perform a sphincterotomy by cutting the external sphincter, thereby allowing the bladder to empty against low pressure in the urethra.

If the patient is able to perform intermittent catheterization and prefers not to wear an external condom catheter, bladder paralysis can be attempted with anticholinergic medications. The most frequently used is oxybutynin, a smooth-muscle relaxant, usually at a dose of 5 mg orally three or four times a day. It acts as an intracellular calcium channel blocker. Another medication used frequently is propantheline bromide in doses of 15 mg orally three times a day. Probantheline is primarily a competitive antagonist at the cholinergic receptor. Together these two agents have a synergistic effect, since each works at different sites. Other anticholinergic agents have no advantage over these two. Tofranil, an imipramine, used primarily in psychiatry, is occasionally fairly effective in its anticholinergic effect on the bladder.

It is essential that vesical pressure be monitored in patients on intermittent catheterization. If the urethral pressure is high, for example 90 cm H_2O, and the bladder pressure reaches 45 or 50 cm, the patient will not leak between catheterizations because the resulting pressure in the bladder is below that of the urethra. However, this is not a "safe" bladder, because the ureter cannot propel urine against a resting pressure above 35 cm H_2O. Hydronephrosis will result any time the resting pressure exceeds 35 cm. It is therefore important to confirm that low intravesical pressure has been attained with medication, when necessary, when intermittent catheterization is the treatment choice.

The common adverse effects of anticholinergic drugs are dry mouth, constipation, and urinary retention. In spinal-cord-injured patients, urinary retention may be the desired effect. Visual disturbances are an indication for discontinuation. Anticholinergics should not be prescribed for patients with glaucoma. These agents should also be avoided in patients with the Shy-Drager syndrome because the episodes of hypotension may be aggravated.

Finally, some patients already have upper-tract damage as a result of their bladder management as practiced 20–30 years ago. Struvite stone formation is the rule. Extracorporeal lithotripsy is one of the most important tools available at this point to avoid end-stage renal failure. Once kidney stones occur as a result of the high pressure transmitted to the kidney and the chronic infection, the course is one of recurring infections and stone formation.

However, extracorporeal shock wave lithotripsy has been a true lifesaver. Previously, such patients required surgical removal of the stone. However, stones and infection would recur, requiring second and third surgical interventions, often resulting in decrease or loss of renal function. These patients came to dialysis because the disease was usually bilateral.

Lithotripsy has forever revolutionized that. We can now treat multiple recurrences. Although it is not a magic cure, since renal function may still deteriorate as a result of chronic infection and stone formation, end-stage renal failure can be delayed.

Questions and Answers

Question: How successful is transurethral sphincterotomy?

Sotolongo: It has a 25%–30% failure rate. The skeletal muscle that is incised may heal readily. Often the sphincterotomy has to be repeated in two or three months, sometimes a few years later.

Question: Does an indwelling catheter prevent high bladder pressure?

Sotolongo: It does prevent high pressure, but at high cost. The indwelling catheter, either urethral or suprapubic, entails three major complications. One is bladder stone formation, and a resultant high propensity to form stones in the upper tract as well. Bladder stones are a bad omen for these patients. The non-life-threatening complications are urethral diverticula and abscess and loss of a testicle as a result of epididymitis. Occasionally, a bladder contracts so completely that it is virtually collapsed. It thus obstructs the upper tract mechanically. Although an indwelling catheter does avoid high bladder pressure, it is not a desirable solution.

Question: What about the new techniques of controlling bladder function electronically?

Sotolongo: I think the question refers to bladder “pacemakers,” which are being studied in California and are becoming somewhat more widespread, although they are still investigational. The procedure involves placing electrodes in the sacral cord and actually stimulating certain nerves that control the external sphincter and bladder. One or the other can be stimulated, so, in theory, one should be able to control bladder and sphincter perfectly. In truth, bladder and sphincter function rely on a complex neurologic system. Stimulating only one nerve can cause other reflexes that may overcome what one is trying to accomplish. Therefore, certain nerve roots have to be cut, resulting in other complications. So, yes, I think the procedure holds future hope, but I do not think it is part of standard therapy at this point, although it may become an effective way of controlling the bladder more physiologically.

Question: Should IVPs be performed yearly on spinal-cord-injured patients?

Sotolongo: If we have studied the patient with urodynamics and we know that the bladder pressure is safe, there is little indication to do an IVP yearly because we have been preventing the initiating insult. One can perform yearly renal ultrasound studies, which are sensitive in detecting hydronephrosis as well as stones. If the renal sonogram is abnormal, we can then go on to the IVP the same year. It is relatively rare, however, that the IVP is abnormal if there is documented low pressure in the bladder.

Pathophysiology of End-Stage Renal Disease in Spinal Cord Injury

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Spinal-cord-injured patients are at increased risk of developing end-stage renal disease. In fact, prior to the 1960s, chronic renal failure was the principal cause of death in as many as 75% of all spinal-cord-injured (SCI) patients. Fortunately, during the past two to three decades, considerable progress has been made in the preservation of renal function and prevention of end-stage renal disease in this population. Progress is clearly reflected in subsequent surveys, which have revealed a steady decline in mortality from renal failure in SCI patients. For instance, the mortality from chronic renal failure among World War II and Korean War veterans, reported in 1974, approximated 45%, whereas that reported for the veterans of the Vietnam conflict was 20% (1, 2). An even lower incidence of about 14% was subsequently demonstrated in a large series of civilian cases followed up by Price (3).

The pathogenesis of chronic renal failure associated with spinal cord injury is complex and multifactorial. Impaired urine flow associated with neuropathic bladder dysfunction plays the central role in the vicious cycle that can lead to chronic pyelonephritis and reflux nephropathy, urolithiasis, and destruction of renal parenchyma.

In a large series of patients with end-stage renal disease due to spinal cord injury studied by our group, all patients without exception had chronic pyelonephritis and chronic active urinary tract infection (4–6). A great majority of these patients had been maintained on indwelling urethral catheters, some on suprapubic catheters; a few underwent surgical diversion. Nephrolithiasis was extremely common, and renal amyloidosis was quite frequent. In addition, reflux nephropathy and hypertensive nephrosclerosis were present in some cases.

Clearly, impaired urinary drainage predisposes to and complicates the treatment of urinary tract infection, which is both facilitated and perpetuated by instrumentation, especially indwelling catheters and subsequent development of nephrourolithiasis. The combination of urinary tract infection and increased intravesical pressure leads invariably to reflux, which further promotes the destruction of renal tissue. The gradual reduction in nephron mass due to the combination of these factors leads to compensatory hyperfiltration and glomerular capillary hypertension, which, in turn, accelerates the rate at which remaining nephrons are lost. This process is marked histologically by initial glomerular hypertrophy, followed by glomerular sclerosis.

Thus, when either untreated or improperly managed, impaired urinary drainage triggers a chain of interrelated events that can result in end-stage renal disease. In addition to the processes described above, renal amyloidosis is also commonly present and further contributes to renal deterioration in these patients. The amyloidosis in this condition is generally of the secondary type associated with chronic infections involving bedsores, osteomyelitis, and possibly chronic active urinary tract infection. Accordingly, prevention and treatment of various infections can preclude the occurrence of secondary amyloidosis, which affects not only the kidneys, but most other organs as well.

Adapted from the author's presentation at the conference "Spinal Cord Injury: Aspects of Specialized Care" held at the Bronx Veterans Affairs Medical Center on April 22, 1991; final manuscript received February 1992. From the Division of Nephrology, Department of Medicine, University of California, Irvine. Address reprint requests to the author, who is Professor and Vice Chairman, Department of Medicine, and Chief, Division of Nephrology, at the Division of Nephrology, UCI Medical Center, 101 The City Drive, Orange, CA 92668.

Based on this review, it is quite clear that SCI-associated chronic renal disease is potentially preventable. The most important step in prevention of renal disease is provision of safe and satisfactory urine drainage while avoiding indwelling catheters and diversion techniques when possible. This is best achieved by promoting spontaneous voiding or, if that is not possible, regular clean intermittent catheterization. The other equally important and related step is prevention and treatment of infection, which directly (chronic pyelonephritis) and indirectly (struvite stone, amyloidosis) promotes destruction of renal tissue. In addition, measures to reduce high intravesical pressures associated with spastic bladder have been advocated by a number of authorities in an attempt to prevent renal tissue damage by vesicoureteral reflux. Struvite urolithiasis, which is caused by the presence of urinary tract infection with urease-producing organisms, itself can perpetuate the infection, cause obstruction, and promote kidney damage. Therefore, every effort should be made to prevent stone disease or vigorously treat it once it has occurred.

Factors Contributing to Chronic Renal Disease in SCI Patients

Factors that contribute to chronic renal disease in spinal-cord-injured patients include:

- Impaired urine flow due to neuropathic bladder dysfunction
- Urinary infection leading to chronic pyelonephritis
- Nephrolithiasis, infection stones, and other calculi
- Reflux nephropathy due to high intravesical pressure and infection
- Progressive loss of remaining nephrons due to glomerular hyperfiltration and hypertension
- Secondary amyloidosis
- Hypertensive arteriolonephrosclerosis (uncontrolled HTN)

Prevention and treatment of infected or uninfected pressure ulcers and osteomyelitis is also important in preventing damage to the kidney and other organs from secondary amyloidosis.

In addition to the listed measures of specific relevance to SCI patients, certain general principles should be considered. For instance, excessive use of analgesics can lead to papillary necrosis and chronic interstitial nephritis and should be avoided when possible. Similarly, caution should be exercised in the use of nephrotoxic agents such as aminoglycoside antibiotics, and control of hypertension, when present, is important to avoid arteriolonephrosclerosis. In this regard, certain agents such as angiotensin-converting-enzyme inhibitors and calcium channel blockers may not only serve to control hypertension, but also to retard the progression of renal insufficiency when present.

Measures to Prevent or Retard Progression of Chronic Renal Failure in SCI Patients

To prevent or retard progression of chronic renal failure in patients with spinal cord injury, the following measures should be taken:

- Provision of safe and effective urine flow
- Prevention or effective treatment of urinary infection
- Correction of high intravesical pressure
- Prevention or treatment of urolithiasis
- Prevention or treatment of pressure ulcers
- Prevention or treatment of chronic extrarenal infections such as pressure ulcers, osteomyelitis
- Control of arterial hypertension
- Avoidance of excessive or prolonged use of analgesics capable of producing analgesic nephropathy
- Caution with the use of nephrotoxic drugs such as aminoglycoside antibiotics

Interpreting Measures of Renal Function. Several important issues need to be considered in interpretation of certain laboratory or derivative data employed to assess renal function in SCI patients (6, 7). For instance, serum creatinine concentration is generally lower in SCI patients than in able-bodied individuals with the same glomerular filtration rate. This is due to lower creatinine production reflecting diminished muscle mass in SCI patients. Therefore, serum creatinine values well within the normal range for able-bodied persons may, in a spinal-cord-injured individual, signify a significant reduction in glomerular filtration rate. The extent of error is proportional to the extent of the associated paralysis and muscle atrophy, being greater in quadriplegics than paraplegic persons. In a recent study, Kaji et al. showed urinary creatinine excretion and creatinine clearance to be markedly lower in a group of spinal-cord-injured patients, serum creatinine ranging between 1.0 and 0.5 mg/dL when compared with a group of able-bodied individuals (8), confirming previous observations. Mathematical formulas devised to predict creatinine clearance in able-bodied individuals using serum creatinine, age, weight, and sex are highly unreliable when employed without modification for SCI populations. We and others have developed correction factors to adapt these formulas to paraplegic and quadriplegic persons (9). Given its limitations, creatinine clearance is a relatively reliable tool for assessing the renal excretory function; however, certain precautions have to be taken to avoid inaccuracies. Clearly, the accuracy of the result is dependent on the precision and completeness of the timed urine collection in all subjects. However, Kaw et al. recently reported a significant fall in urine creatinine concentration from the time of collection to the point of assay in SCI patients with certain urinary infections (10). This particular phenomenon compounds the complexity of this test and interpretation of its results.

With regard to other laboratory measurements, we have found certain differences between SCI and able-bodied patients with end-stage renal disease. As a group, the SCI patients had significantly lower hematocrit and serum bicarbonate and albumin concentrations. In contrast, they had higher urine output and proteinuria than their able-bodied counterparts. Many SCI patients had nephrotic-range proteinuria while on maintenance dialysis. This is a relatively unusual phenomenon, since glomerular leakage of protein usually declines in parallel with the decline in nephron mass as reflected by the fall in glomerular filtration rate. However, renal amyloidosis represents an exception to this rule and accounted for persistent heavy proteinuria in our patients.

Avoiding Hyperkalemia. Hyperkalemia is a major and potentially life-threatening complication of renal insufficiency. Usually progressive loss of nephron mass associated with chronic renal insufficiency triggers a number of adaptive processes to mitigate the rise in extracellular potassium concentration. These include readjustments in glomerulotubular balance in the remnant nephrons, leading to an increase in potassium excretion. In addition, the large intestine assumes a significant role in potassium homeostasis by secreting large quantities of potassium (as much as 50% of potassium intake) into the feces. These adaptive processes may be disturbed in SCI patients, with the attendant risk of life-threatening hyperkalemias. Owing to the predominant tubulointerstitial nature of renal disease in SCI patients, adaptive rise in tubular secretion of potassium (and often H^+) may be defective in this population. Moreover, colonic motility and sphincteric disorders, which frequently give rise to constipation and fecal impaction in SCI patients, can interfere with the adaptive colonic potassium secretion. Accordingly, SCI patients with severe renal insufficiency may be at greater risk of hyperkalemia than their able-bodied counterparts. This issue should be considered in the management and monitoring of these patients, and special attention should be given to bowel care and impaction control in this setting.

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Obesity Surgery:

Dietary and Psychosocial Expectations and Reality

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Abstract

Psychosocial and dietary habits have been compared in patients considering (Pre $n = 33$) or who had (Post $n = 32$) surgery for morbid obesity. Failure of conventional diets was attributed to lack of self-discipline (Pre 92% [22/24] vs. Post 87% [20/23], NS). Consumption of fast foods fell (Pre 70% [23/33] vs. Post 16% [5/32], $p < 0.0001$). Preoperative patients had unrealistic social expectations. They exaggerated the prospect of improved friendship (Pre 67% [22/32] vs. Post 34% [11/21], $p < 0.05$), erroneously anticipated better sex (Pre 78% [25/32] vs. Post 50% [15/30], $p \leq 0.05$), predicted better acceptance at work (Pre 85% [23/27] vs. Post 50% [15/30], $p \leq 0.05$), and misanticipated improved relationship with their partner (Pre 77% [20/26] vs. Post [47% 8/17], $p \leq 0.05$). Two factors predicted becoming employed following surgery: age (became employed [$n = 5$] 28 ± 2 years vs. remained unemployed [$n = 12$] 44 ± 4 years, $p < 0.05$) and percentage of excess weight lost (became employed 76 ± 11 vs. remained unemployed 51 ± 7, $p < 0.05$). The free support group was "useful" (17/17), yet only 5% attended regularly. Patients considering obesity surgery had specific unrealistic psychosocial expectations. They infrequently availed themselves of postoperative professional help. We identify the features associated with gaining employment.

Morbid obesity (1), a major health problem (2), afflicts seven and one-half million people in the United States (3). The morbidly obese have obesity-related diseases (2, 4–6), difficulties with medical insurance (7), and social (8, 9), psychological (9), and employment-related difficulties (10). Accumulating evidence suggests that conservative dietary therapy does not result in long-term weight loss for this population (11, 12). As a result, gastrointestinal surgical therapy for morbid obesity is increasingly being employed (13, 14). A body mass index ≥40 is the suggested level above which surgery may be considered (14).

Vertical banded gastroplasty (VBG) (15) is a gastric reduction procedure that limits the quantity of food that can be consumed (16, 17). Unlike some other procedures in current use (18), VBG has no malabsorptive component. The weight loss (15, 19–21), preoperative expectation (22), and physiological (23) and psychological outcome of VBG (9, 24) have been reported.

The purpose of this study is to compare psychosocial and dietary expectations prior to surgery with the reality that follows VBG. We specifically addressed fat intake, dietary and weight changes, subjective impressions, and employment history. We show that patients often have unrealistic expectations and are recalcitrant to long-term professional follow-up. The likelihood of becoming employed following surgery is directly related to being younger and losing more weight.

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TABLE 1
Demographic Characteristics

	Preoperative ($n = 33$)		Postoperative ($n = 32$)	
	No.	%	No.	%
Age (years)				
<20	2	6	3	9
20–29	9	27	5	16
30–39	14	42	6	19
40–49	7	21	12	37
50–59	1	3	5	15
60–69	0	0	1	3
Sex*				
Male	1	3	5	16
Female	32	97	27	84
Marital status				
Married	10	30	9	30
Single	17	52	11	37
Divorced	3	9	3	10
Separated	2	6	3	10
Widowed	1	3	4	13
Ethnicity*				
Black	3	9	4	13
Hispanic	21	64	10	31
White	9	27	18	56
Education level (completed)				
None	0	0	1	3
K–6	2	6	0	0
Jr high school	10	30	7	22
High school	16	48	15	47
College	3	9	6	19
Graduate school	2	6	3	9
Employment**				
None	17	52	4	13
Part-time	1	3	1	3
Full-time	9	27	17	53

* $p \leq 0.05$.
** $p \leq 0.01$.

Methods

Preoperative (Pre $n = 33$) and postoperative (Post $n = 32$) patients of one surgeon (RJG) were interviewed either at their initial office visit (Pre) or by telephone (Post). Postoperative patients were randomly selected from a list of all 187 postsurgical patients. All patients who were contacted participated in the study. Data were collected from April 1990 through September 1990. Patients were interviewed for 30 min (JGR). Follow-up phone calls were made to confirm and complete information.

Following a pilot study on 10 preoperative patients, a finalized 175-item questionnaire (approximately 50 questions) (22) was used. In the resulting final questionnaire, the subjects addressed were demographics (8%, $n = 14$), obesity history (11%, $n = 20$), dietary habits (25%, $n = 44$), weight loss (21%, $n = 37$), quality of life (25%, $n = 44$), and obesity-related diseases (9%, $n = 15$). Demographics included age, sex, education level, occupation, marital status, and ethnicity.

Dietary habits were obtained through 24-h dietary recall and cross-checked using reports of daily and weekly food frequency. This interview method has been described (25) and shown to have validity in assessing the average intake of a group (26, 27). Similar results have been demonstrated for establishing mean intake for the face-to-face interview method (used for preoperative patients) versus the telephone interview method (used for postoperative patients) (28). Patients were interviewed in detail about the name and description of each food item eaten (brand names when possible), preparation method, and portion size, using household measures (teaspoons, tablespoons, cup sizes). These measures have been shown to enhance the ability of the interviewee to estimate food portion sizes accurately (29). Weight history over the year preceding the interview and expectations of weight loss maintenance were addressed. "Support systems" items identified the professional or nonprofessional person sought when dietary or related problems arose. "Quality of life" items addressed health, personal appearance, employment, social relationships, and self-esteem.

Certain aspects of this study have been reported elsewhere (22). Included were obesity history, health-related aspects of obesity, weight loss, and its maintenance.

Statistical Analyses. Data from the completed questionnaires were entered into Excel (Microsoft, Redmond, WA) and Statview 512+ (Abacus Concepts) using Mac Plus Computer (Apple Computer, Cupertino, CA). Percentage of ideal body weight was calculated using the 1983 Metropolitan Life Tables (medium frame). Dietary analysis was performed using Nutritionist III (Analytic Software, Salem, OR). The database of this program contains 2,025 foods and 58 nutrients. The 24-h dietary recall information was analyzed for grams and percentage of carbohydrate, protein, fat, and saturated fat. These were compared to the *Dietary Guidelines for Healthy American Adults* of the American Heart Association (30). Statistical analysis was by chi-squared, unpaired t-tests or parametric ANOVA as appropriate. Data are presented as mean ± SEM. Significance was accepted at $p < 0.05$.

Results

Sample. The preoperative subjects were interviewed at their initial office visit. The postoperative group were interviewed from 4 to 84 months (24 ± 4 mean ± SEM) following surgery. Similarities in demographic characteristics were found in male/female ratios, age, educational levels, marital status, and presurgery weight of both groups. Weight (Pre 287 ± 9 lb vs. Post 291 ± 13 lb, NS), body mass index (Pre 49.6 ± 1.6 vs. Post 48 ± 1.7, NS), and percent of ideal body weight (Pre 218 ± 6 vs. Post 211 ± 6 NS) were similar. Males were heavier than females (≥225% of IBW: males 67% [4/6] vs. females 34% [20/59], $p \leq 0.01$).

A large percentage of the population was Hispanic (48%) and female (89%). There were significantly more females than males in both groups (**Table 1**). The mean age was 36 years (Pre 33 ± 1.6 years vs. Post 38.6 ± 2.6 year, NS), with 8% (5/65) of patients below the age of 20, and 11% (7/65) of patients above the age of 50. Statistical differences between groups were observed in ethnicity and employment (Table 1).

Nutrition. Weight regain following conventional diets was ascribed by patients to lack of self-discipline (Pre 92% [22/24] vs. Post 87% [20/23], NS). The absence of support systems was additionally implicated as a reason for failure (Pre 70% [16/23] vs. Post 54% [14/26], NS). A minority of patients had consulted a dietitian before requesting surgery (Pre 16% [5/32] vs. Post 6% [2/32], NS).

Preoperative diets were higher than recommended guidelines in simple sugars, processed meats, and fast food products (30). Diets contained ≤20% of recommended complex carbohydrates and fiber (average 5 g in both groups) (30). Postoperative patients generally consumed the same types of food but in greatly reduced quantities (22). Foods high in fat, such as cake, cookies, and ice cream, remained favorite items for both groups.

Patients' caloric intake fell significantly following surgery (calories: Pre 5,283 ± 356 vs. Post 1,622 ± 95, $p \leq 0.001$) (22). No difference was found in the proportion of fat intake (% fat: Pre 40% vs. Post 37%, NS). The number of subjects eating fast foods fell precipitously following surgery (Pre 70% [23/33] vs. Post 16% [5/32], $p < 0.0001$).

The dietary differences between patients who lost <49.9% or ≥50% of their excess body weight following surgery are presented in **Table 2**. Differences in protein between the groups may result from the decrease in total calories. The postoperative group preferred diet soft drinks. Other differences in nutritional choices between the two groups were negligible (data not presented).

TABLE 2
Analysis of 24-hour Dietary Recall of Postoperative Patients by % of Excess Weight Loss

	Excess wt loss ≥49.9% (pt no. 21)	Excess wt loss ≤50% (pt no. 9)	*p*
Protein (g)	55 ± 6	80 ± 12	≤0.05
Carbohydrate (g)	187 ± 14	226 ± 30	NS
Fat (g)	66 ± 7	81 ± 8	NS
Total calories	1,500 ± 106	1,800 ± 183	NS

Weight loss of the postoperative group was 104 ± 14 lb (22). The preponderance of weight loss occurred in the first year following surgery, which is in agreement with previous studies (19, 31, 32) (actively losing: 0–12 months [$n = 14$] 100% vs. 13–84 months [$n = 18$] 42%, $p \geq 0.01$). Patients thought they would maintain weight loss following surgery (Pre 97% [32/33] vs. Post 94% [30/32], NS). In reality, 44% of postoperative patients were actively losing weight, and 50% had stabilized their weight. Postoperative patients said that they would not be able to control their weight if surgery were reversed (Post 86% [26/31]).

Both groups "strongly agreed" that their goal was to lose 50% of excess weight in one year following surgery (Pre 97% [32/33] vs. Post 97% [29/30], NS). Sixty-six percent [21/32] of postoperative patients lost and maintained ≥50% of their excess body weight over a 4–84–month period (22).

Employment. More individuals were employed in the postoperative group (Pre 30% [10/33] vs. Post 56% [18/32], $p < .05$) (Table 1). Two factors identified those who became employed fol-

TABLE 3
Postoperative Employment Changes

	Became employed	Remained unemployed
No. of patients	5 (29%)	12 (71%)
Mean age	28 ± 2.4*	44 ± 4.4
Male/female	1/4	3/9
Time postop, months	10 ± 2	13 ± 4.4
% excess wt loss	76 ± 11*	51 ± 7

Mean ± SEM. *$p \leq 0.05$.
17 patients unemployed prior to antiobesity surgery.

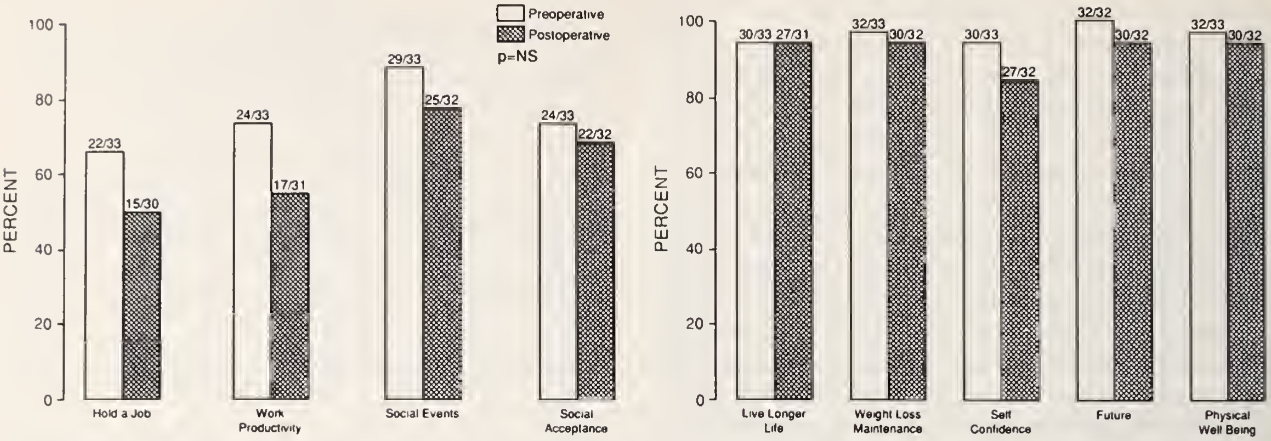

Fig. 1. Elements of quality of life on which expectations of preoperative patients were relatively realistic as compared to expectations of postoperative patients.

lowing surgery (Table 3). They were younger (became employed [$n = 5$] 28 ± 2 years vs. remained unemployed [$n = 12$] 44 ± 4 years, $p < 0.05$) and had lost more weight (% excess weight lost: became employed 76 ± 11 vs. remained unemployed 51 ± 7, $p < 0.05$).

Quality of Life. Concordance between preoperative and postoperative group expectations was evident on many aspects of quality of life (Fig. 1). By contrast, preoperative patients had unrealistically high expectations, as compared to the expectations of postoperative patients, for acceptance at work, ability to make and keep friends, better sex, and better relationships (**Fig. 2**).

Support Systems. A professionally guided monthly support group session is available free to all patients. Twenty-eight percent of preoperative patients and 53% of postoperative patients had attended at least once. Regular attendance among postoperative patients is 5%. Of the 17 patients who had attended, all said it had been helpful. This study did not address the reasons for the limited attendance.

Following surgery, there was an increase in family and friends who approved of the operation. Family (Pre 79% [27/33]) and friends (Pre 88% [29/33]) had been told about the proposed surgery. Only 57% (18/33) of family and 52% (17/33) of friends approved. Six representatives of disapproving family and friends, when recontacted following surgery (87% [6/7]), had become supportive.

Discussion

This study provides insights for the bariatric surgeon and other health professionals to better prepare the patient for the reality of life following surgery. We document an improved quality of life and better employment prospects following surgery for morbid obesity. Postoperatively, these patients are not availing themselves of accessible professional dietary counseling. All patients who have attended the supervised monthly support group attest to its usefulness. Yet only ≤15% do so. We identify the critical period, one year following surgery, when education may be optimally provided. We emphasize reducing fat intake in our postoperative counseling.

In many areas, patients have realistic expectations (Fig. 1); however, we find they are unrealistic about sex, friends, and acceptance at work (Fig. 2). Our subjects were recruited in a random manner. Follow-up studies to validate these observations may be conducted on either the same individual prior to and following surgery or pair-matched individuals.

Unsatisfactory weight loss following gastric restrictive surgery has been ascribed to excess "sweet" consumption (19). It is possible that fat is of equal or greater importance. Body fat is directly related to fat intake (33), and morbidly obese people may be especially efficient at lipid storage (34). Our patients' consumption of fat is similar to that of the general American population (35). Fat comprises ~69% of calories from cake, ~70% of calories from candy, and ~48% of calories from ice cream (36). Patients may be unaware of the need to decrease their fat intake (30), unaware of the hidden grams of fat they are consuming, or unwilling to change their dietary habits. The continued high consumption of fat may be due, in part, to the palatability of fat foods and the satiety fat induces (37).

Body weight may be decreased by lowering dietary fat without restricting quantity of food

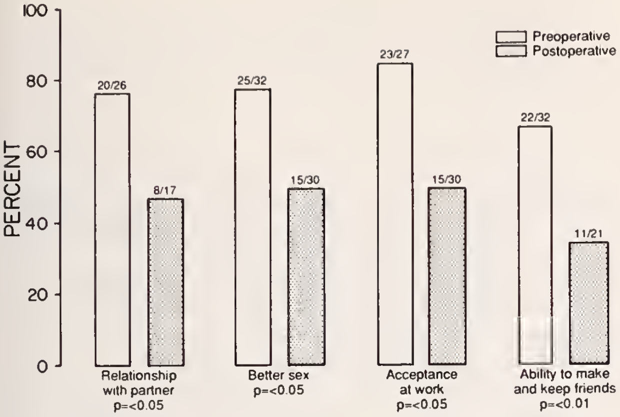

Fig. 2. Elements of quality of life on which expectations of preoperative patients diverged widely from expectations of postoperative patients.

consumed (38). We show that postoperative patients continue to consume a diet high in fat (Table 2). Our postoperative counseling now emphasizes decreasing fat intake to ≤40 g/day. At the initial preoperative office visit, patients are given an informational pamphlet to assist in this aim. After surgery, they receive a reference book that itemizes the fat content of most foods (39).

There is an association between ethnic origin and obesity (40). Obesity-related diseases are prevalent in medical clinics used by Hispanics (7). In this study, a large percentage of the patient population is Hispanic. We ascribe this to the ethnic mixture in the New York metropolitan area, as well as to patient-patient referral patterns. In the preoperative group they constitute the majority (64%, 21/33), whereas in the postoperative cohort their representation falls to 31% (10/31) (Table 1). This may have resulted in biased results. However, an ethnically stratified analysis of dietary habits did not show any differences (data not presented). This may mean that the population, self-selected by weight, do indeed have similar dietary habits. Alternatively, in order to identify ethnic-dependent differences, a larger number of subjects will need to be studied.

In the United States the prevalence of obesity in men and women is about equal (9). We confirm that a disproportionate percentage (41) of those attempting to control their weight are females (and see the *New York Times,* Nov. 24, 1991). We show that when men do seek help, they are heavier than women. Social stigma may, in part, encourage more females to seek surgical weight control assistance (42). Our patients view lack of self-discipline as the most important factor for not maintaining previous weight loss. Although multiple attempts at dieting had been made, for some of the patients perioperative dietary counseling by our registered dietitian may be their first professional contact. However, this deficiency cannot be ascribed solely to the lack of opportunity to associate with professionals, as only 5% of patients attend the free, professionally run, monthly support group. We ascribe the lack of support of family and friends prior to surgery predominantly to fear of death at surgery.

Postoperative patients stated that they are consuming 25% of the calories they ate prior to surgery (22). However, the ratio between carbohydrates, protein, and fat did not change. Nonsignificant changes in consumption of these nutrients before and after surgery have been observed in other studies (43). Patients' dietary mix is low in dietary fiber and high in fat (22).

Remarkably, postoperative patients have vastly reduced the total amount of fast foods consumed. This may be a positive change in dietary habits. More probably, it may be ascribed to the enforced behavior modification, vomit avoidance, induced by the operation (22).

Patients have unrealistic goals for long-term weight loss (22). We confirm that weight loss is maximal in the first year following surgery (19, 32). Success in maintaining weight loss may, in part, depend on continuing dietary and/or other support systems (44, 45). Nevertheless, our results concur (14, 15, 19, 46) that surgery is the optimal therapy for this population at present.

Our patient populations confirm a very high unemployment rate in the population of the morbidly obese (10). This may be ascribed to reluctance to hire the morbidly obese (10) and to poor body image (47). Societal prejudice may also play a role (42). Improvement at work follows vertical banded gastroplasty (41, 48). We show that patients who became employed were younger and had lost a higher percentage of their excess body weight than those who remained unemployed. The implications to society of an effective treatment for the young obese population who are on welfare is of obvious importance.

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Phase II Trial of Etoposide, Carboplatin, and Ifosfamide as Salvage Therapy in Advanced Ovarian Carcinoma

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Abstract

A phase II study combining etoposide with carboplatin and ifosfamide as salvage therapy in advanced ovarian cancer was undertaken. Objective responses were achieved in 37.5% of 16 evaluable patients with a mean progression-free interval of 8.6 months. Stable disease was present in 25% of patients; in 37.5% of patients the disease progressed on salvage. Based on original response to front-line therapy, patients were classified as being platinum-sensitive (group I) or platinum-refractory (group II). Clinical response to salvage therapy was seen in 44.5% of group I patients, but in only 28.6% of group II patients. This difference was not statistically significant. When a more precise definition of platinum sensitivity was applied, clinical responses were seen in 54.5% of group I patients, but no responses were noted among group II patients ($p < 0.05$). Platinum sensitivity appeared to be an important factor in achieving a response with this regimen. This combination was well tolerated, myelotoxicity being the dose-limiting toxicity encountered. No life-threatening, nonhematologic toxicities were seen. One death occurred secondary to nadir sepsis. The combination of etoposide, carboplatin, and ifosfamide is an active salvage regimen in patients with advanced ovarian carcinoma; however, severe myelotoxicities and inability to produce long-term responses underscore the need for continued trials to find a more durable salvage regimen.

The use of platinum combination therapy in patients with advanced stage III and IV ovarian cancer produces clinical response rates of greater than 75% (1–3). Surgical complete responses, however, fall below 40% (1, 4, 5), and the outlook for patients with >2 cm residual disease is restricted (6). The relapse rate among patients who achieve a complete response by pathologic examination is estimated at 45%–65%, most of these relapses occurring within two years of second-look laparotomy (7).

Several regimens have been proposed as salvage therapy for those patients whose disease progresses during front-line treatment or in whom carcinoma recurs following successful treatment for advanced ovarian cancer. These regimens have resulted in clinical responses of 10%–50%, with progression-free intervals ranging from 6 to 12 months (8–11). The optimal salvage regimen, however, has not been defined, because to date no regimen has produced durable responses. Current investigations are therefore focusing on second-generation analogs of active first-line agents. Among the analogs that have been tested, carboplatin (JM8), a cisplatin analog, and ifosfamide, an analog of cyclophosphamide, have emerged as agents demonstrating therapeutic activity in patients with advanced ovarian carcinoma (12, 13).

The podophyllotoxin derivative etoposide has also been evaluated as a single agent in the treatment of advanced ovarian cancer, producing clinical response rates of 22% (14), and it appears to be synergistic with cisplatin, as demonstrated with L1210 leukemia cells (15). Carboplatin, a

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TABLE 1
Characteristics of 17 Patients

		No. of pts
Age		
Median	56.8 yr	
Range	45–50 yr	
Prior therapy	AP	12
	CP	2
	CAP	2
	C-IP cisplatin	1
Cisplatin		
Mean	800 mg	
Range	465–1650 mg	
Prior salvage therapy, range	1–3 courses	7

AP, adriamycin, cisplatin; CP, cytoxan, cisplatin; CAP, cytoxan, adriamycin, cisplatin; C-IP, cisplatin, intravenous high-dose cytoxan, intraperitoneal cisplatin.

cisplatin analog, has been found to be as effective as cisplatin in the primary treatment of ovarian cancer and has been proposed as the first choice in retreatment for patients who have had a previous response to cisplatin (16). As primary treatment for advanced stages III and IV ovarian cancer, ifosfamide produces responses of 33% (17); however, its importance in salvage regimens may lie in its ability to produce responses in patients with platinum-refractory ovarian cancer (18).

Combining three agents with known individual activity in advanced ovarian carcinoma, we undertook a phase II study utilizing etoposide with carboplatin and ifosfamide as salvage therapy for patients with advanced ovarian carcinoma that has recurred following successful treatment or has progressed during treatment with platinum-containing agents.

Materials

Seventeen patients with stages III and IV ovarian cancer who had received primary treatment with a platinum-containing regimen following initial surgery were entered on a phase II trial utilizing etoposide, carboplatin, and ifosfamide as a salvage regimen. The protocol was approved by the Institutional Review Board of the Mount Sinai Medical Center, and informed consent was obtained from all patients prior to administration of chemotherapy.

Eligibility criteria included histologically proven advanced epithelial cancer and pretreatment with a platinum-based regimen. All patients had an expected survival of greater than 12 weeks and Karnofsky performance status of at least 40. Measurable disease was present in all patients as determined by measurements on computed-tomography scans. Baseline hematologic data for entry into this protocol included white blood cell count more than 3500/mm^3 and platelet

TABLE 2
Status Following First-Line Cisplatin Therapy

Pt. no.	Stage	Second look	Time to recur	Site of recurrence	Response to salvage
			Group I platinum sensitive		
1	3	Negative	24 mo	Abdomen	CR × 4 mo
2	3	Negative	24 mo	Pelvic l.n.	CR × 5 mo
3	3	Negative	24 mo	Carcino	PR × 5 mo
4	3	Negative	17 mo	Liver	Stable × 5 mo*
5	3	Negative	28 mo	Pelvis	Dead—Tx comp.
6	3	Refused	38 mo	Carcino	CR × 4 mo
7	3	Micro +	10 mo	Pelvis	Progression*
8	3	Micro +	7 mo	Pelvis	Progression*
9	3	Micro +	11 mo	Carcino	Stable × 3 mo*
10	4	Micro +	20 mo	Porta hep	Stable × 5 mo*
			Group II platinum refractory		
1	3	None	6 mo	Abdomen	CR × 5 mo†
2	3	None	6 mo	Pelvic l.n.	CR × 4 mo
3	3	None	Progression	Pelvis	Progression*†
4	3	None	Progression	Liver, ascites	Progression
5	4	None	3 mo	Pelvis, abd	Progression†
6	4	None	4 mo	Pelvis	Progression
7	3	None	4 mo	Liver, carcino	Stable × 4 mo*†

Micro, microscopic disease; abd, abdomen; CR, complete response; PR, partial response; l.n., lymph nodes; carcino, carcinomatosis; porta hep, porta hepatus.

* Treatment with at least one salvage regimen before entering on protocol.

† Secondary debulking attempted.

counts greater than 125,000/mm^3. Normal hepatic function and serum creatinine less than 1.5 mg/dL were also required.

The dosages for these three agents were as follows: ifosfamide, 1.2 g/m^2 days 1–3; etoposide, 100 mg/m^2 days 1–3; carboplatin, 100 mg/m^2 days 1–3.

The uroepithelial protector sodium-2-mercaptoethane sulfonate (MESNA) was administered each day that ifosfamide was given, with the aim of preventing hemorrhagic cystitis (19). MESNA was administered intravenously in three equally divided doses prior to administration of ifosfamide and repeated at four hours and eight hours following ifosfamide infusion. All patients were admitted for the duration of the chemotherapy. Toxicities were graded according to the Gynecologic Oncology Group criteria for toxicities. Dose reductions were made for grade 3–4 toxicities as follows: 10% reduction if nadir counts of platelets and white blood cells were 25,000–50,000/mm^3 and 500–1,000/mm^3, respectively, and 25% reduction if platelet count was less than 25,000/mm^3 and white blood count less than 50/mm^3.

Treatment was delayed more than four weeks until platelet counts increased to at least 100,000/mm^3 and white blood cell counts to 3,000/mm^3 or greater.

Responses were defined as complete (CR) if there was disappearance of all physiologic and radiologic evidence of disease, with sustained absence of CA-125 levels where applicable, or as partial (PR) if there was a decrease greater than 50% in the product of the two largest perpendicular dimensions of existing lesions in the absence of new lesions. The disease was defined as stable if there was no evidence of new tumor growth or less than 25% increase in the product of the two largest dimensions of an existing tumor mass or the onset of new effusions and lesions.

All patients were followed up with weekly laboratory data, monthly examinations, and radiologic studies when indicated.

TABLE 3
Survival of Patients Treated with Salvage Therapy

No. of pts	Response to salvage	Mean survival (range)	No. pts alive (%)
6	1 PR, 5 CR	14.3 mo (9–23+ mo)	4 (66.7)
4	Stable dz	15.5+ mo (7–23+ mo)	2 (50.0)
6	Progression	7.7 mo (4–12 mo)	0 (0.00)

PR, partial response; CR, complete response; stable dz, stable disease.
One patient died of treatment-related complications.

Results

All 17 patients entered on this study were evaluable for toxicity and response (**Table 1**). All patients were previously treated for either stage III or stage IV ovarian cancer.

Two groups of patients were identified in the study population, based on response to first-line cisplatin therapy (**Table 2**). Group I consisted of patients who demonstrated a clinical response to first-line cisplatin treatment (platinum sensitive). Patients were considered to demonstrate clinical platinum sensitivity if they were clinically free of disease at the end of therapy and

TABLE 4
Comparison of Response to Salvage Therapy of Platinum-Sensitive and Platinum-Refractory Patients Using Original and Revised Definitions of Sensitivity

	Clinical response (CR + PR)	Stable dz	Dz progression	p†
	Original Definition‡			
Group I: sensitive (9 pts)*	4 pts (44.5%)	3 pts (33.3%)	2 pts (22.2%)	
Group II: refractory	2 pts (28.6%)	1 pt (14.3%)	4 pts (57.1%)	NS
	Revised Definition‡			
Group I: sensitive (11 pts)*	6 pts (54.5%)	3 pts (27.3%)	2 pts (18.2%)	
Group II: refractory	0 pts (0.00%)	1 pt (20.0%)	4 pts (80.0%)	.05

CR, complete response; PR, partial response; Dz, disease.
* 1 patient died of treatment-related complications.
† Statistical testing using χ^2 test of independence $df = 2$, p-value <.05.
‡ Original definition of platinum sensitivity: patients who demonstrated clinical response to first-line cisplatin by being clinically free of disease at end of therapy and were eligible for second-look laparotomy. Revised definition: patients who, after treatment with first-line platinum, are clinically and chemically free of disease and remain so for up to 6 months.

were eligible for second-look laparotomy. Ten platinum-sensitive patients (59%) were identified, nine of whom underwent a second-look laparotomy.

Group II consisted of patients who were platinum refractory. All demonstrated either progression of disease during therapy or measurable recurrence within six months of completion of a platinum-containing regimen. Seven patients (41%) were determined to be platinum refractory.

Response to Therapy. Table 3 shows overall response to therapy among 16 of the patients who were eligible for evaluation of response. Table 4 compares the responses between group I (platinum sensitive) and group II (platinum refractory) patients.

Hematologic Toxicity. A total of 12 patients (70.6%) required at least one dose reduction for hematologic toxicity. Fifty percent (6 patients) experienced severe thrombocytopenia, with a mean nadir platelet count of 27.7 K (range 3 K–49 K). In 45% (5 patients), therapy was complicated by severe neutropenia. Three of these patients were treated for granulocytopenic fevers. In one, sepsis was documented, and despite aggressive medical management in an intensive care unit, the patient succumbed to infection. Blood transfusions were administered to 8 patients; hemoglobin counts below 6.5 g/μL were seen in 2 patients.

Nonhematologic Toxicity. All patients experienced grade 3 alopecia; however, gastrointestinal, genitourinary, and neurologic toxicities were all mild. In no patient was therapy discontinued because of any nonhematologic toxicity.

Discussion

This clinical trial was designed to investigate the efficacy of the combination of etoposide, carboplatin, and ifosfamide for use as salvage therapy in advanced ovarian carcinoma. Alone, each agent has produced clinical responses of 22%–50% as first-line therapy in patients with advanced ovarian carcinoma (14, 16, 17). The mechanism of action and toxicities of these agents vary, and although various combinations utilizing one or more of these drugs have been reported, this is the first report combining these three agents in the treatment of recurrent or persistent ovarian carcinoma.

Etoposide exerts its cytotoxic effect by inhibiting DNA synthesis through the formation of a complex with DNA and topoisomerase II, the DNA-unwinding enzyme. As such, it causes the arrest of cells in the late S or early G2 phase (20, 21). Its only significant side effect is myelotoxicity; thus it can be combined with other cytotoxic agents and be administered safely to heavily pretreated patients. When etoposide has been combined with cisplatin as salvage therapy in ovarian cancer, clinical response rates of 53% have been demonstrated (11).

Carboplatin, like its parent cisplatin, binds covalently to DNA, thus disrupting DNA function. In the treatment of ovarian cancer, both agents are equally effective; however, carboplatin has a spectrum of toxicities that differs from that of cisplatin, resulting in much less nephrotoxicity, neurotoxicity, and emesis (22, 23). It is established that as salvage therapy, cisplatin will produce responses in alkylating-agent-resistant ovary cancer, in patients who have had intensive prior therapy, and in patients demonstrating previous sensitivity to cisplatin (24–26); however, severe toxicities on the renal and neurological systems have limited its use. Like cisplatin, carboplatin is also effective in the treatment of platinum-sensitive ovary cancer. Although clinical studies indicate cross-resistance between these two drugs, it may be incomplete; responses to carboplatin in cisplatin-refractory ovary cancer have been demonstrated in approximately 5% of patients (27). Ifosfamide appears to be a reasonable alternative in the management of these patients.

In this study, the 28% clinical response rate seen among the cisplatin-refractory individuals at first glance appears to support incomplete cross-resistance between carboplatin and cisplatin. This response rate is also higher than that reported by Ozols et al and Colombo et al, who saw no responses to high-dose carboplatin among patients who failed to respond to cisplatin regimens (28, 29). In an attempt to explain this discrepancy, we reviewed the responses among the cisplatin-refractory patients in this study and found that the only responses in this group were in patients whose measurable disease occurred six months following first-line therapy. It appears from this observation that patients with recurrences at six months following first-line cisplatin behave more like cisplatin-sensitive individuals. We therefore propose a definition of platinum-sensitive patients as those who, following treatment with first-line platinum, are clinically and chemically free of disease and remain so for up to six months following first-line therapy. The importance of a precise definition of platinum response among ovarian cancer patients has recently been addressed (30).

Using our new definition, we compared the response to salvage therapy between platinum-sensitive and platinum-refractory patients and found that the difference between these groups was statistically significant (Table 4). The adjusted data also appear more compatible with Ozols' findings. The benefit of ifosfamide in producing responses among patients whose disease progresses on cisplatin is not seen in this small group of patients.

Using this combination of etoposide, carboplatin, and ifosfamide in patients previously treated with at least one platinum-containing regimen, we have demonstrated that the dose-limiting toxicity is clearly hematologic; this has been similarly demonstrated with the use of carboplatin in previously treated patients (29). Serious hematologic toxicity resulting in dose reduction occurred in over 70% of patients, and infection secondary to severe myelosuppression was present in over 5% of patients. Neurotoxicity, in particular somnolence, confusion, and aggravation of preexisting psychiatric conditions, has been reported in approximately 5% of patients receiving ifosfamide (31). None of these effects were observed in this population, even among those patients with psychiatric disease that predated entry into this protocol.

The present study indicates that when used in combination as salvage treatment for advanced ovarian cancer, etoposide, carboplatin, and ifosfamide produce clinical response rates of over 35%, with a mean progression-free interval of 8.6 months. The combination appears to be beneficial in patients who have demonstrated previous platinum sensitivity. These results demonstrate that this combination has activity as a salvage regimen in advanced ovarian cancer, and in a well-selected population can equal the clinical response rates of 53% seen with the use of etoposide and cisplatin, as previously reported from this institution. The associated morbidity and mortality with this regimen are, however, higher than with etoposide and cisplatin alone. Continued trials, using other triple combinations in an attempt to achieve a more durable response while decreasing morbidity and mortality, will therefore continue. We stress the importance of identifying those patients who demonstrate previous platinum sensitivity, because these patients appear to benefit most from retreatment with platinum analogs.

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The Enteroinsular Axis and Endocrine Pancreatic Function in Chronic Alcohol Consumers:

Evidence for Early Beta-Cell Hypofunction

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Abstract

Chronic alcohol consumers may have, as judged by functional criteria, exocrine as well as endocrine pancreatic dysfunction, the latter represented by a decreased insulin response to an oral glucose load. To investigate whether this decreased insulin response was due to an ethanol-induced beta-cell dysfunction or to an ethanol-induced dysfunction of the enteroinsular axis, we determined glucose, insulin, and C-peptide plasma concentrations following an oral and an intravenous glucose load in 16 healthy volunteer nonalcohol consumers and in 10 chronic alcohol consumers. In each group, total integrated response for glucose did not significantly change whether glucose was given orally or intravenously, indicating isoglycemic glucose loads. The total integrated response values for insulin in the alcoholic group following both glucose loads as well as C-peptide plasma concentrations were significantly lower than in the control group. Moreover, in both groups the insulin TIR values following the oral glucose load were significantly greater than the values obtained following the intravenous glucose load, indicating an incretin effect. These results indicate that the decreased insulin response observed in alcoholics was not caused by a dysfunction of the enteroinsular axis because it also occurred following an intravenous glucose load, but by an ethanol-induced beta-cell dysfunction because C-peptide and insulin were proportionally decreased in this group.

It is assumed that pancreatic hypersecretion of bicarbonate and protein following secretin-cholecytokinin (S-CCK) stimulation is the first detectable functional alteration in asymptomatic alcoholics (1). As we have previously reported (2), many asymptomatic alcoholic subjects whose S-CCK test showed normal secretion or hypersecretion of bicarbonate had a decreased oral glucose-induced insulin response that suggests that the endocrine dysfunction might occur as early as the exocrine dysfunction during the disease process, although not always simultaneously (2). Therefore, normal results in an S-CCK test on those subjects does not exclude ethanol-induced pancreatic injury.

It is well established that insulin secretion is partially influenced by a complex mechanism, the so-called enteroinsular axis (EIA), which comprises the action of gastrointestinal hormones (incretin effect), adrenergic, cholingeric and peptidergic neural transmission (3). Approximately 50% of the insulin released into the portal circulation is degraded during its first circulation through the liver, whereas C-peptide, which is also released by beta cells in concentrations equimolar to insulin, is not (4). Therefore C-peptide plasma concentrations better reflect the beta-cell function than do plasma insulin concentrations.

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TABLE

Glucose, Insulin, and C-Peptide Concentrations in Plasma after an Oral and an Intravenous Glucose Load in Healthy Controls and Alcoholics (Mean ± SE)

Factor in plasma	Control (n = 16)	Alcoholic (n = 10)
Glucose (mmol.L^{-1})		
Fasting	4.3 ± 0.2	4.1 ± 0.2
120-min post oral glucose	4.5 ± 0.4	4.2 ± 0.4
Glucose TIR (mmol.L^{-1}.120 min^{-1})		
After oral load	613 ± 43	632 ± 42
After IV load	646 ± 39	642 ± 34
Insulin TIR (nmol.L^{-1}.120 min^{-1})		
After oral load	43 ± 5	21 ± 2*
After IV load	28 ± 3†	12 ± 1*†
Oral:IV ratio	1.6 ± 2.1	1.8 ± 1.0
C-peptide (nM)		
After IV load at corresponding insulin peak rise	1.9 ± 0.2	1.1 ± 0.1‡
C-peptide:insulin ratio	2.4 ± 0.2	3.9 ± 1.2

TIR, total integrated responses.

* Significantly different ($p < .05$) from corresponding value for oral test in both groups by Student's *t* test.

† Significantly different ($p < .005$) from corresponding value in controls by Student's *t* test.

‡ Significantly different ($p < .05$) from corresponding value in controls by Student *t* test.

As ethanol can affect the pancreas (5) as well as the liver and the gut (6), the decreased insulin response observed in alcoholics could be a consequence of (a) an increased hepatic insulin degradation, (b) impaired EIA function, or (c) beta-cell dysfunction, or of a combination of these states.

In the present study we determined glucose, insulin, and C-peptide plasma concentrations following an oral and an intravenous (IV) glucose loads in chronic alcohol consumers to examine the EIA and beta-cell functions in these patients.

Materials and Methods

An oral (OGTT) and an intravenous (IVGTT) glucose tolerance test were carried out in 15 male and 1 female healthy volunteer nonalcohol consumers (defined as occasional ethanol intake, always less than 50 g of pure ethanol), average age 35 (20–48) years, and in 10 chronic alcohol consumers (called in this paper alcoholic subjects), average age 43 (27–53) years, who had neither clinical nor laboratory evidence of hepatic disease or diabetes and have been consuming at least 50 g of pure ethanol daily for more than 2 years (2). The average daily ethanol intake was 276 g (50–480) for an average period of 21 (8–25) years. The average total ethanol intake (daily intake × 365 × years) was 1,679.0 (548.0–2,920.0) kgs.

Measures of protein electrophoresis, prothrombin time, bilirubin, ALT, AST, alkaline phosphatase, and amylase, as well as plain abdominal X-ray, were normal in all subjects. A diet containing at least 100 g of carbohydrate was given to all subjects during a 3-day period prior to glucose tolerance tests which were performed on subsequent days, the OGTT being the first. After the subjects fasted overnight, blood samples were collected for determination of fasting plasma glucose levels. For the OGTT, a solution containing 100 g of glucose was given by mouth, and blood samples were collected at 30, 60, 90, and 120 minutes. For the IVGTT, a 50% (w/v) glucose solution (0.5 g/kg body weight) was administered by IV bolus injection and blood collected at 1, 3, 5, 10, 20, 30, 40, 60, and 120 minutes (7). Plasma glucose levels were immediately determined by an oxidase method (God Papp, Boehringer Mannheim Biochemicals, Indianapolis, IN, US) and absorbances determined by a spectrophotometer (505 nm). Plasma samples were stored at −70°C for insulin (determined as previously described) (2) and for C-peptide radioimmunoassay determinations (kit from Immunonuclear Corporation, Stillwater, MN, US). For each subject, C-peptide concentration was determined in the plasma samples that corresponded to the insulin peak rise following the IV glucose load. Total integrated responses (TIR) for glucose and insulin were calculated as described by Besterman et al. (8).

Statistical analyses were assessed by two-way analysis of variance (ANOVA), and where the ANOVA showed a significant difference, the groups at each time point were compared using the Student's *t* test. Informed consent was obtained from each subject.

Results

Plasma glucose concentrations at fasting and 120-min after oral glucose load were normal in both groups **(Table)**. Moreover, in each group TIR values for glucose following an oral glucose load did not differ from those following an IV glucose load, indicating isoglycemic glucose loads (Table).

In the control group, following the oral glucose load, the plasma insulin concentration was maximal at 30 min (fivefold increase) and decreased progressively to half-maximal at 120 min. In the alcoholic group there was a similar pattern of increase, but with a significant decrease in the insulin curve (Fig. 1) and consequently a decreased insulin TIR (Table).

In both groups, following the IV glucose load, insulin concentrations rapidly increased to maximal at 5 min (sevenfold increase) and progressively decreased to basal values at 120 min, but the alcoholic group showed a distinct decrease in the insulin curve (**Fig.** 2) and consequently decreased insulin TIR (Table). Consequently, the alcoholic group showed significantly lower insulin: glucose ratios in both tests (data not shown).

In each group, the insulin TIR value following the oral glucose load was significantly greater than that following the IV glucose load, indicating an incretin effect in both groups (Table).

The C-peptide mean value obtained for the alcoholic group was significantly lower than that obtained for the control group, whereas the C-peptide:insulin ratio for the two groups was not significantly different (Table).

Discussion

The present study illustrates that chronic alcohol consumers have a significantly decreased insulin response following an oral glucose load, confirming our previous observation (2), and illustrates as well that the decreased insulin response also occurs following an IV glucose load.

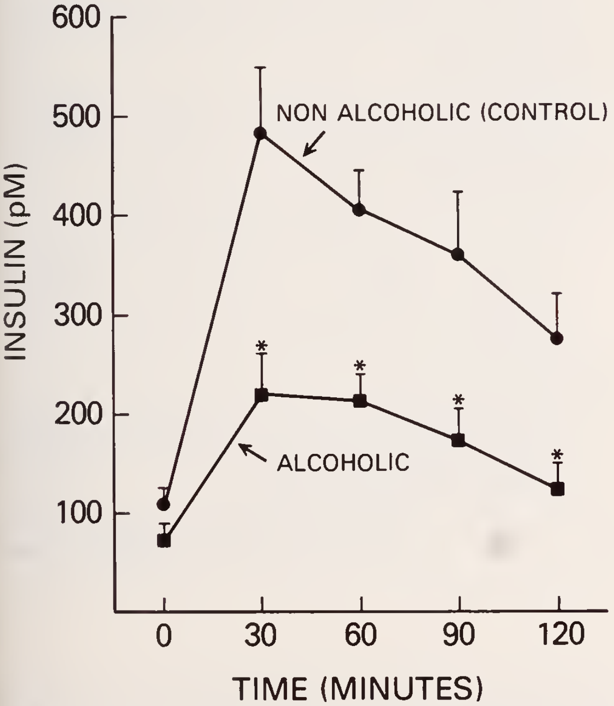

Fig. 1. Plasma concentrations of insulin in response to oral glucose load (100 g) in nonalcoholic (n = 16) and alcoholic (n = 10) subjects. Values for plasma insulin concentrations were determined in triplicate and results given are mean for the number of subjects specified. *Significantly different ($p < .05$) from corresponding control value by Student's *t* test.

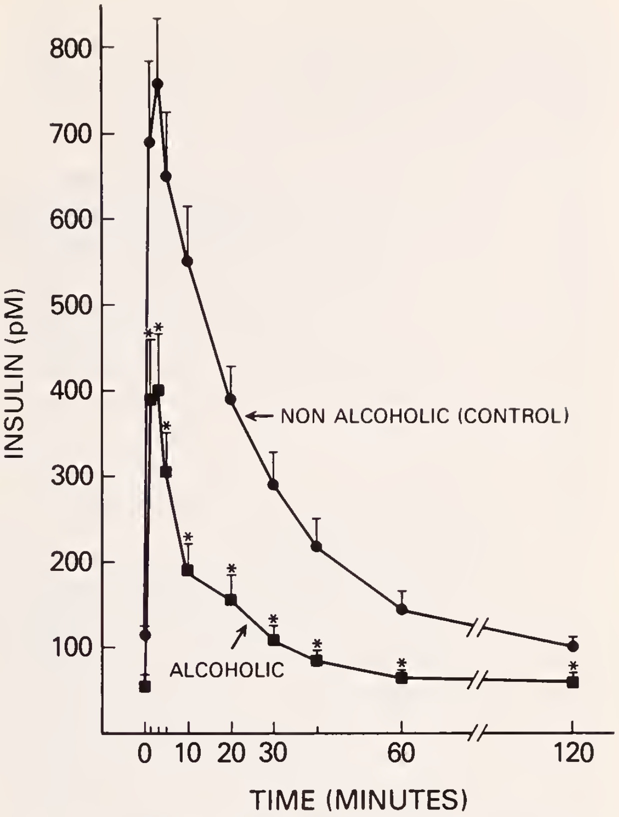

Fig. 2. Plasma concentrations of insulin in response to intravenous glucose load (0.5 g/kg body weight) in nonalcoholic (n = 16) and alcoholic (n = 10) subjects. Values for plasma insulin concentrations were determined in triplicate and results given are mean for the number of subjects specified. *Significantly different ($p < .05$) from corresponding control values by Student's *t* test.

Our present results showed an incretin effect in both groups and a decreased insulin response to both oral and IV glucose loads in the alcoholic group, making it unlikely that ethanol-induced dysfunction of the EIA could account for the decreased insulin response observed in these patients. Normal EIA function has also been reported in different situations, such as chronic pancreatitis (9) and experimentally induced atrophy of the exocrine pancreas (10).

Because ethanol can affect the liver (6), it is conceivable that ethanol could alter insulin uptake by the liver and thus account for the decreased insulin response observed in these alcoholics. However, a previous study (11) has estimated the fractional hepatic uptake of insulin from the molar ratio of insulin and C-peptide and found that ethanol decreased the hepatic uptake of insulin after an IV glucose load, which could account for an eventual alcohol-induced increase in insulin plasma concentrations but could not account for an alcohol-induced decrease in insulin plasma concentrations. Moreover, in alcoholic patients with cirrhosis of the liver, glucose intolerance and high plasma insulin concentrations are usually found (12). In contrast, in the present study we found a decreased insulin response to a glucose load with normal glucose tolerance, since none of the control or the alcoholic subjects met the National Diabetes Data Group criteria (13) for either diabetes or impaired glucose tolerance on the oral glucose tolerance test performed. These findings, taken in conjunction with those reported previously on the action of ethanol on glucose uptake by the liver (9) and in alcoholics with cirrhosis of the liver (12) argue against the possibility of ethanol-induced liver damage accounting for the decreased insulin response observed in alcoholics.

The present finding of C-peptide and insulin plasma levels proportionally decreased in alcoholics indicates that the decreased insulin response has occurred as a consequence of an alcohol-induced beta-cell dysfunction. The mechanism by which ethanol chronically ingested could affect beta-cell function is not known. It has been reported that alcohol induces degenerative changes in human pancreatic acinar cells, suggesting a direct toxic effect of ethanol (14). It has also been proposed that ethanol chronically ingested increases intrapancreatic cholinergic tone (15), with consequent pancreatic dysfunction. However, no data is available to support either mechanism accounting for an alcohol-induced beta-cell dysfunction.

In conclusion, the present results indicate that chronic alcohol consumers may have decreased insulin response to oral and IV glucose as a consequence of ethanol-induced beta-cell dysfunction. Therefore, glucose-induced insulin response should be considered a complementary procedure for the detection of ethanol-induced pancreatic dysfunction in alcoholics, particularly in those whose S-CCK test results are normal.

Acknowledgments

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Thoracic Herniated Discs:

Review of the Literature and 12 Cases

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Abstract

In comparison with herniations of lumbar or cervical intervertebral discs, symptomatic thoracic disc herniation is rare. Between 1986 and 1991, 12 cases of thoracic herniated discs were treated at The Mount Sinai Hospital, New York City. Most patients had back pain or myelopathy. Nine of the disc herniations occurred at the lowest six thoracic interspaces. Eight patients underwent costotransversectomy and discectomy. Seven of these patients improved without complication. One patient was subsequently found to have a spinal arteriovenous malformation below an incidental herniation that had been identified by magnetic resonance imaging. Because of the nonspecificity of the signs and symptoms, as well as the prevalence of incidental herniations on imaging, a careful clinical and radiologic correlation is mandatory when diagnosing this uncommon pathology.

ALTHOUGH symptomatic herniation of a thoracic intervertebral disc is extremely uncommon, it merits attention for several important reasons. First, the increased sensitivity provided by new diagnostic techniques has heightened the need for enhanced clinical specificity (1). Second, there has been significant progress in surgical techniques and approaches to the thoracic spine (2–15). Finally, thoracic disc herniation is one of the few notable causes of cord compression that is reversible.

According to Carson et al., the first description of a herniated thoracic disc occurred over 150 years ago (16). However, it was not until 1931 that Elsberg described the first surgically treated patients (17). At that time these lesions were frequently termed “eccondroses” or “ventral extradural chondromas.” So rare was their occurrence that by 1960, the world literature included a total of only 95 cases (17). The estimated annual incidence is one case of thoracic disc herniation per one million population (16).

Materials and Methods

Twelve patients were treated in the Departments of Neurosurgery and Neurology of The Mount Sinai Hospital in New York between January 1986 and June 1991 (**Table 1**). In addition to a detailed neurologic examination, all patients were evaluated by computed tomography (CT), magnetic resonance imaging (MRI), or myelography (**Fig. 1**). There were eight men and four women, ranging in age from 33 to 72 years, with a mean age of 53.

The most common presentation was back pain or myelopathy. Myelopathy included progressive paraparesis, hyperreflexia, and a pinprick level. Two patients developed urinary retention. The duration of symptoms ranged from 10 days to 8 years.

Nine of the herniated discs occurred at the lower six thoracic interspaces (Fig. 1). Of the discs occurring at the higher levels, two were at T5-6 and one was at T3-4. Only two cases were associated with prior trauma.

Eight patients were treated by costotransversectomy and discectomy. This technique has been

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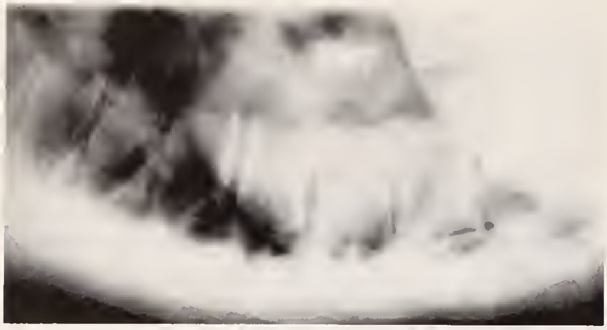


Fig. 1. Thoracic myelogram shows epidural defect at T9-10 interspace causing posterior displacement of thecal sac.

well described elsewhere (15). Seven of these patients had relief of pain and significant improvement of neurologic deficit and were able to walk on discharge. There were no complications in these seven patients. Three patients were managed conservatively and were lost to follow-up; one patient is considering surgery.

In one patient, who had rapidly progressive paraparesis and myelopathy, MRI diagnosed a T3-4 herniated disc. Despite costotransversectomy and discectomy, this patient failed to improve. A spinal arteriovenous malformation was later discovered by myelogram three levels below the herniated disc.

Discussion

Herniations of the intervertebral disc in the thoracic spine are much less common than those in the cervical or lumbar spine. An incidence of between 0.2% and 5.3% of thoracic discs among all herniated discs has been described, with a mean of 0.67% (**Table 2**).

Thoracic disc herniation is predominantly a disease of middle age. In a review of the literature, 80% of 288 patients were between the third and fifth decades when initially consulting a physician, with a peak of 33% in the fourth decade (18). The youngest patient was 12, the oldest 79.

The role of trauma has been debated as a cause of herniated thoracic discs. Two of the largest series found trauma to play an etiologic role in about 25% of cases (n = 128). However, Russell found that men under 40 years had a 53% incidence of trauma whereas all others had a 17% rate, suggesting that younger men represent a distinct group in which trauma plays a significant role (19).

Most series have found a male predominance of herniated thoracic disc. Review of 10 series disclosed a 60% prevalence among men and a 40% prevalence among women (**Table 3**), a finding similar to that in this series: 67% men and 33% women.

Most series find a predominance of central or centrolateral herniated discs (**Table 4**). In a review of 288 cases, the most common level was T11-12 (26%), and 75% of the thoracic discs occurred below T8 (17). It has been suggested that the more frequent localization in the lower tho-

TABLE 1

Clinical Features of 12 Herniated Thoracic Discs

#	Age/ sex	Duration of symptoms	Signs and symptoms	HNP level	Treatment	Outcome
1	65M	3 wk	Back pain Myelopathy	T8-9	Costotransversectomy	Improved
2	43F	8 yr	Back pain Myelopathy	T7-8	Conservative	Unchanged
3	51M	8 wk	Myelopathy	T8-9	Costotransversectomy	Improved
4	72M	6 wk	Back pain Myelopathy	T10-11	Costotransversectomy	Improved
5	71M	10 d	Back pain Myelopathy	T7-8	Costotransversectomy	Improved
6	60M	12 wk	Myelopathy	T3-4	Costotransversectomy	Worsened
7	54M	4 wk	Back pain Myelopathy	T10-11	Costotransversectomy	Improved
8	53F	6 wk	Back pain Paresthesia	T5-6	Costotransversectomy	Improved
9	50F	8 wk	Back pain Incont. ×2d	T6-7	Costotransversectomy	Improved
10	50M	4 wk	Myelopathy	T5-6	Conservative	LTF
11	37F	2 yr	Back pain	T9-10	Conservative	LTF
12	33M	8 yr	Back pain Myelopathy	T11-12	Conservative	LTF

LTF, lost to follow-up; F, female; M, male.

TABLE 2

Incidence of Thoracic Discs among All Discs

Series	Discs		
	Thor	Total	% thor
Mixter and Barr 1934 (34)	1	19	5.3
Love and Walsh 1938 (35)	6	113	5.3
Love and Kiefer 1950 (26)	12	5,500	0.2
Logue 1952 (27)	11	250	4.4
Abbott and Retter 1956 (36)	11	600	1.8
Arseni and Nash 1960 (17)	12	2544	0.47
Love and Schorn 1965 (20)	17	3683	0.46
Russell 1989 (19)	18	400	0.45
Total	88	13,109	0.67

Thor, thoracic.

racic spine is due to the increased mobility and torsion stresses in this area (17, 18).

Difficulties in Diagnosis. Unlike lumbar and cervical disc disease, thoracic disc herniation is not associated with any distinct syndrome. As might be expected, a central disc herniation is likely to produce a myelopathy, whereas a lateral herniation is apt to cause radicular symptoms. In addition, the findings are dependent on the level of the herniation. Further confounding the diagnosis is the nonspecificity of the most common finding: back pain. This pain is variable in its presentation, occurring locally or in a radicular fashion. When it is radicular, a herniated thoracic disc can be mistaken for cardiac, thoracic, or abdominal pathology. Some patients have reportedly been treated for gallbladder disease for a misdiagnosed thoracic disc (18).

In Love and Schorn's series of 62 patients (20), a correct preoperative diagnosis was made in only 13 cases. In the era of MRI and CT, this low preoperative diagnostic rate is unlikely, but it does underscore the variability and nonspecificity of the neurologic findings. After pain, the most common symptoms are sensory disturbance and motor weakness. The sensory abnormalities include both dysesthesias and paresthesias. Bladder involvement is a rare initial symptom but will ultimately occur in one-third of patients (18).

In most series the duration of symptoms varies from a few weeks to years. Histories as long as 26 years have been reported (18). The symptoms can be constant or intermittent, or may progress gradually or rapidly (21).

Plain X-rays can be helpful in the presence of a calcified thoracic disc. In a review of 200 cases of thoracic spine films, McAllister and Sage found disc space calcifications in 4% (22). However, in patients with herniated thoracic discs, calcifications are present in up to 75%. Therefore, the presence of a calcified disc may suggest the presence of a herniation, but a normal plain X-ray of the thoracic spine does not exclude a thoracic disc protrusion.

Although myelography and computed tomography have been the diagnostic procedure of choice (**Figs. 1, 2**), MRI has recently been used with greater frequency to evaluate patients with herniated thoracic discs (**Fig. 3**). Several reports have extolled the effectiveness of MRI in localizing symptomatic thoracic disc herniations (23, 24).

Despite high sensitivity for detecting thoracic discs, MRI may have poor specificity. One study examined thoracic MR images obtained from a group of 48 oncology patients who were not known to have herniated discs (25). Using only

TABLE 3

Prevalence by Sex and Age of Thoracic Herniated Discs

Series	Females No. (%)	Males No. (%)	Age range (X = mean)
Love and Kiefer 1950 (26)	9 (53%)	8 (47%)	26–73 (X = 48)
Kite et al. 1957 (28)	5 (50%)	5 (50%)	18–68 (X = 41.5)
Love and Schorn 1965 (20)	28 (46%)	33 (54%)	19–73
Benson and Byrnes 1975 (2)	7 (32%)	15 (68%)	33–66 (X = 48)
Sekhar and Jannetta 1983 (14)	3 (25%)	9 (75%)	26–66 (X = 50)
Maiman et al. 1984 (6)	6 (26%)	17 (73%)	16–69 (X = 45)
Arce and Dohrman 1985 (18)	94 (40%)	142 (60%)	12–73 (X = 45)
Bohlman and Zdeblick 1988 (3)	8 (42%)	11 (58%)	25–73 (X = 36)
Otani et al. 1988 (9)	5 (22%)	18 (78%)	28–75 (X = 48)
Russell 1989 (19)	31 (46%)	36 (54%)	16–79 (X = 49)
Total	196 (40%)	294 (60%)	12–79

TABLE 4
Location of Disc Herniation

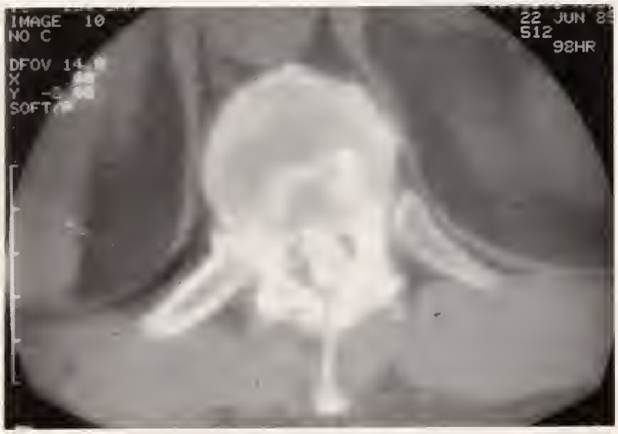
Series	Central or centro-lateral	Lateral
Love and Kiefer 1950 (26)	14 (77%)	3 (23%)
Perot and Munro 1969 (11)	57 (63%)	34 (37%)
Arce and Dohrman 1985 (18)	126 (68%)	60 (32%)

T1-weighted images, these authors found a 14.5% prevalence of incidental thoracic disc herniations. This high prevalence of incidental herniations underscores the need for a careful evaluation before making the diagnosis of symptomatic thoracic disc herniation. Given the lack of a distinct clinical syndrome, confirmation of suspected herniations may require further study, including CT-myelography in many patients.

Surgical Treatment. The surgical treatment of thoracic disc disease involves problems unlike the surgical treatment of cervical or lumbar disc disease. For example, the thoracic cord has little subarachnoid space and a tenuous blood supply. In addition, displacement of the cord is limited by the dentate ligaments. Centrally herniated thoracic discs are frequently hard and calcified and are often adherent to the dura. Sometimes, dural erosion occurs and a fragment of disc becomes embedded in the spinal cord.

In response to these surgical challenges, many approaches to the thoracic spine for the treatment of herniated discs have been described, including laminectomy, pediculectomy with joint resection, the lateral extracavitary approach, the lateral gutter approach, costotransversectomy, and thoracotomy (2–16).

Fig. 2. Below Postmyelographic CT scan at T9-10 shows calcified disc causing posterior displacement and disruption of dye column. **Fig. 3. Right** T1-weighted saggital (TR = 20, TE = 600) MRI reveals significant compression of spinal cord by low signal mass at thoracic interspace level consistent with calcified disc.



The results of most early surgical series are disappointing. Until 1960, the standard treatment consisted of decompressive laminectomy with or without extradural or intradural removal of the disc. Of the 17 cases of Love and Kiefer reported in 1950, only 1 patient improved and none completely recovered (26). In 1952, Logue described 11 patients of whom only 6 improved (27).

Kite et al. reported one case in 1957 of a physician who had a T11-12 discectomy, presumably by laminectomy (28). His paraparesis was unimproved and his pain worsened to the point that he could no longer practice medicine and became addicted to narcotics. "A unilateral prefrontal lobotomy was performed . . . with little effect upon the pain and was followed by the subsequent development of postoperative epilepsy. Within 5 years after removal of the disc, this physician underwent complete dissolution of his personality and died" (28). Despite the bad experience reported by most series, laminectomy continues to be advocated by some (1).

In 1971, Carson et al. described the lateral-gutter approach, which combined laminectomy

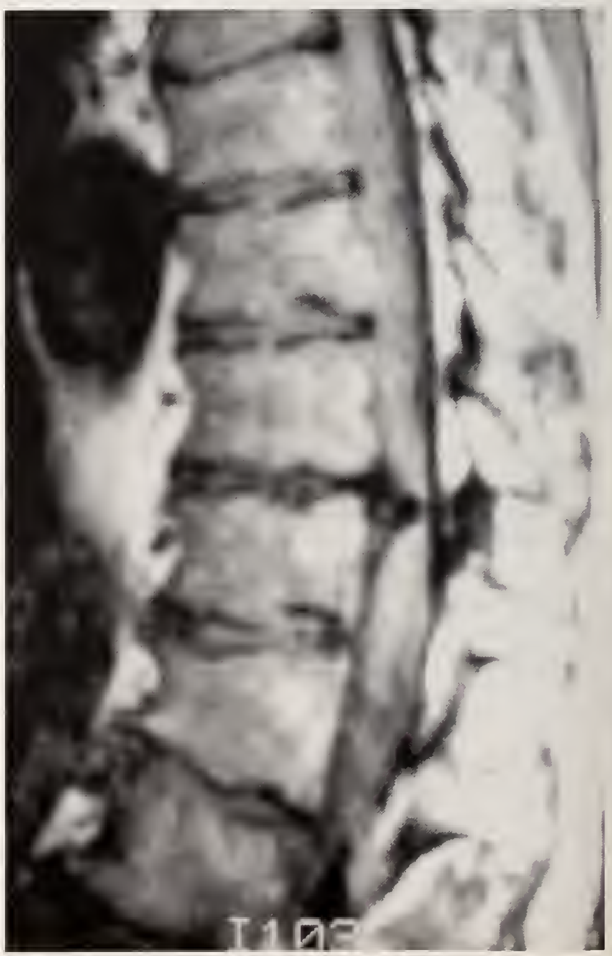


TABLE 5
Rates of Surgical Success from Combined Series (17, 18)

Approach	Total	Cured	Improved	Unchanged	Worse	Died
Posterior	135	22 (16%)	57 (42%)	14 (10%)	37 (28%)	5 (4%)
Lateral and posterolateral	83	28 (34%)	42 (51%)	11 (13%)	2 (2%)	
Transthoracic	52	22 (42%)	25 (48%)	2 (4%)	3 (6%)	

with removal of a considerable portion of the facets (16). They noted that this allowed them to approach the disc space very nearly laterally and reported improvement in 12 of 14 cases. Patterson and Arbitt reported a modified technique whereby the patients were operated on by a midline incision with removal of a facet and pedicle, followed by discectomy and then laminectomy (10). They described 3 patients; 2 were cured and 1 improved.

Costotransversectomy was first described by Menard in 1900 for the surgical decompression of tuberculosis (2). Hulme applied this technique to thoracic disc herniations and reported improvement in 4 of 6 patients operated on (29). Costotransversectomy provides a more lateral visualization and therefore a greater opportunity for anterior maneuvering than does the lateral-gutter technique. Although both interbody fusion (6) and spinal instrumentation (30) have been advocated following costotransversectomy to prevent instability, long-term follow-up of patients without stabilization finds no evidence of vertebral slippage (15).

The lateral approach is an extension of costotransversectomy and involves a more lateral rib resection. Although the approach was first described by Capener, it was Larson who named it the "lateral extracavitary approach" and reported it in the treatment of traumatic lesions of the thoracolumbar spine (31). By 1984, Maiman et al. reported 23 patients treated by this approach (6). Seventeen had significant pain relief and 20 were improved neurologically.

Crafoord et al. reported the first right-sided transthoracic disc removal (32). The patient, who had spastic paraparesis, made a complete recovery. In 1969, Perot and Munro (11) and Ransohoff et al. (12) simultaneously reported a total of 5 successful anterolateral decompressions by thoracotomy. More recently, Otani et al. reported a series of 23 patients in all of whom favorable outcomes were achieved with a transthoracic extrapleural approach (7). Others have found results comparable to those of costotransversectomy (3, 33). However, some remain skeptical of this approach owing to the extensive nature of the surgery and the potential for significant complications (30).

Conclusions

Because the manifestations of thoracic herniated discs are protean, the diagnosis is often highly dependent on radiographic studies. Given a significant incidence of asymptomatic thoracic herniations identified by MRI, great care must be employed to avoid making a misdiagnosis (as occurred in one case described here). It is therefore recommended that myelography with CT be employed in addition to MRI in the following patients: those whose signs and symptoms do not localize the lesion to a specific level; those in whom the herniated disc occurs in the upper half of the thoracic spine; and those with a coexistent disease that might otherwise be responsible (e.g., metastatic carcinoma, neurofibromatosis).

Although few surgeons continue to advocate a posterior surgical approach, the treatment of herniated thoracic discs remains controversial. And although many still prefer the various posterolateral approaches, an increasing number of surgeons are employing a transthoracic approach. Some evidence suggests that the transthoracic approach may offer better access to centrally herniated calcified discs (**Table 5**). At this time, the decision on whether to use a posterolateral or an anterolateral approach should depend on the training and experience of the surgeon.

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Screening for Human Immunodeficiency Virus and Sexually Transmitted Diseases in an Inner-City Colposcopy Clinic

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Abstract

Among patients attending an inner-city colposcopy clinic, the prevalence of *Chlamydia trachomatis* was 22/375 (5.0%), *Neisseria gonorrhoeae*, 3/375 (0.8%), and seropositivity for syphilis, 10/375 (2.7%). In addition, 13/261 (5.0%) of asymptomatic women agreeing to voluntary human immunodeficiency virus (HIV-1) antibody screening were HIV-1 seropositive. Our data support incorporating screening for and education on sexually transmitted diseases and HIV into the work of our colposcopy clinic.

Traditionally, colposcopy clinics have had a narrow focus as screening centers for cervical cancer. The importance of a sexually transmitted pathogen, human papilloma virus (HPV), in the etiology of cervical dysplasia and neoplasia has been recognized; however, the precise role that HPV plays in these disease processes remains undefined (1–3).

The appreciation of the contribution of sexually transmitted HPV to cervical disease led us to evaluate whether our colposcopy clinic should routinely screen patients for the presence of other sexually transmitted diseases (STDs), including the human immunodeficiency virus (HIV-1).

Materials and Methods

The Mount Sinai Medical Center's colposcopy clinic accepts referrals from the hospital-based gynecology clinic and from other local health agencies that serve the East Harlem community. Approximately 300 new cases are referred yearly for evaluation of Papanicolaou (Pap) smear abnormalities, including persistent inflammatory atypia, evidence of human papilloma virus infection, cervical dysplasia, or cervical carcinoma.

From January 1, 1990, through May 1991, all new clinic referrals received individual counseling concerning STD transmission, including HIV-1, and the need for risk reduction behavior. A questionnaire, completed by the interviewing author for each patient, included sociodemographic information, a gynecologic and STD history, and identification of high-risk behaviors for HIV-1 acquisition. Patients accepting STD screening had cervical samples assessed for *Chlamydia trachomatis* by an antigen detection kit (Gen Probe, San Diego, CA) and for *Neisseria gonorrhoeae* by culture. *N. gonorrhea* specimens were collected on modified Thayer-Martin media (Becton Dickinson, Cockeysville, MD) and processed by standard laboratory techniques. In addition, a repeat Pap smear was performed on all patients. Serum samples for syphilis were tested by the rapid plasma reagin (RPR) card test (Becton Dickinson, Cockeysville, MD), with confirmation of positive test results by MHA-TP (Fujireba, Tokyo, Japan). Those accepting voluntary screening for HIV-1 had antibody testing with a standard enzyme-linked immunosorbent assay (ELISA); all positive results were confirmed by Western blot analysis.

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TABLE 1

Results of Sexually Transmitted Disease Screening among 375 Women at an Inner-City Colposcopy Clinic

Age (yr)	No. of pts	Positive results *Chlamydia* No. (%)	 Gonorrhea No. (%)	 Syphilis No. (%)
13–19	44	8 (18)	1 (2)	0 (0)
20–29	170	11 (6.5)	2 (1.2)	8 (4.7)
30–39	100	2 (2)	0 (0)	1 (.27)
40–49	33	1 (3)	0 (0)	0 (0)
50 +	28	0 (0)	0 (0)	1 (.27)
Total	375	22 (5.9)	3 (0.8)	10 (2.7)

Results

A total of 375 patients were seen during the study period; all agreed to gonorrhea, *Chlamydia*, and syphilis screening, and 261/375 (70%) accepted HIV-1 antibody screening. Of those who refused or were ineligible for HIV-1 antibody screening, 5 were known to be HIV-1 seropositive, 1 initially refused testing but was subsequently identified as seropositive, and 4 reported recent negative antibody screens. Results of STD screens are reported by age group in **Table 1**.

In the population screened, the prevalence of *C. trachomatis* was 5.9% (95% CI 3.5%–8.3%), of *N. gonorrhoeae*, 0.8% (95% CI 0%–1.7%), and of positive results on serologic tests for syphilis, 2.7% (95% CI 1%–4.3%). Of those who tested positive for syphilis, 6/10 (60%) had no prior history of syphilis.

Of the 261 women agreeing to voluntary HIV-1 antibody screening, 13/261 (5%) (95% CI 2.4%–7.6%) were identified as seropositive with one additional test reported as inconclusive. HIV-1 risk behaviors were identified by reviewing answers from both the initial screening questionnaire and the follow-up posttest counseling interview. Of the newly identified HIV-1 seropositive women, 5/13 (38%) had a history of injection drug use (IDU), 4/13 (31%) had sexual partners who were HIV-1 seropositive or had known high-risk behaviors, and 4/13 (31%) had a history of multiple sexual partners. Therefore, 62% appear to have acquired their infection by heterosexual contact. There were no differences in the proportion of patients accepting screening among the different age groups, and all newly identified HIV-1-seropositive patients were between the ages of 20 and 39. There were no positive screening tests for *N. gonorrhoeae, C. trachomatis,* or *Treponema pallidum* among the newly identified HIV-1-seropositive women.

Among the newly identified HIV-1-seropositive women, 11/13 underwent colposcopic examination and directed cervical biopsies. No cases of cervical carcinoma were detected, and 7/11 patients had biopsies with a histologic appearance consistent with HPV infection (**Table 2**). In the HIV-1-infected women, discrepancies of greater than one grade in cytology and histology results were not demonstrated.

TABLE 2

A Comparison of Pap Smear Results and Cervical Biopsies in 13 HIV-1-Infected Women

Pt no.	Pap smear	Biopsy result
1	Class III	CIN I
2	Class III	Inflammation
3	Class III	CIN I–II
4	Class III	CIN I
5	HPV	Koilocytosis
6	Class III	Koilocytosis
7	Class III	CIN II, CIN II on ECC
8	Class II	CIN I, koilocytosis
9	Class II	Inflammation
10	Class III	CIN III
11	HPV	Koilocytosis
12	Class III	CIN II
13	HPV	Inflammation

CIN, cervical intraepithelial neoplasia; HPV, human papilloma virus; ECC, endocervical curettage.

Discussion

Patients in our colposcopy clinic demonstrated a high rate of infections with STD pathogens. The infections identified do not necessarily represent newly acquired infections but reflect cumulative STD exposure of those patients. The most frequent infection seen was *C. trachomatis,* with rates of 18% and 6.5%, respectively, among women 13–19 and 20–29 years of age. In other populations studied, rates of infection have varied from 3%–5% in asymptomatic women to over 20% in women in STD clinics (4–10). A recent survey in Great Britain found that 23% of patients referred to a colposcopy clinic from both STD and non-STD clinics were infected with *C. trachomatis* and that the majority of patients were asymptomatic (11). The small numbers of syphilis and gonorrhea infections detected may reflect the lower prevalence of these diseases in our community and are consistent with rates noted in other colposcopy clinics (11).

Among asymptomatic women accepting HIV-1 antibody screening, 5% were identified as seropositive; 8/13 (62%) were suspected of acquiring their infection through heterosexual contact. HIV-1 serosurveys of other populations of reproductive-age women within our institution have revealed a 16% seroprevalence rate in patients admitted with pelvic inflammatory disease (12) and a 2.7% seroprevalence rate in prenatal clinic patients (13). In New York City, a HIV-1 seroprevalence rate of 10% has been reported from another inner-city colposcopy clinic (14).

Trends in the epidemiology of HIV-1 transmission in women are disturbing. A review of epidemiologic trends from an inner-city STD clinic has revealed a twentyfold increase in HIV-1 seroprevalence during the past 10 years, the sharpest increases reported being among African-Americans, women, and adolescents (15). Increases in the ratio of female to male cases among those reported with AIDS and the strong association between the presence of genital ulcer disease, a common problem in sexually active women, and HIV-1 acquisition further underscore the risks to women (16–18).

The high prevalence of HIV and other STDs in our colposcopy clinic population suggests that all patients seen in our clinic should undergo STD and HIV counseling and screening. This finding may be generalizable to other comparable inner-city colposcopy clinics, where comprehensive STD and HIV education, screening, and treatment programs may help decrease the heterosexual spread of these diseases. Monitoring trends in STD and HIV prevalence in these clinics may provide important epidemiologic information about the heterosexual spread of these diseases.

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Case Report:

Evolution of a Type B Aortic Dissection following Renal Artery Angioplasty

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Abstract

Percutaneous renal artery angioplasty is an accepted treatment for renal artery stenosis. A variety of complications have been reported related to this procedure. The authors report a case of Type B aortic dissection occurring immediately following renal artery angioplasty, a previously unreported complication of renal artery angioplasty. A mechanism for this complication in this patient is postulated.

During the past 10 years percutaneous angioplasty has become the standard of treatment for renovascular hypertension caused by renal artery stenosis. Reported complications include occlusion of the renal artery (secondary to thrombosis, dissection, or embolization), perforation of the renal artery (that is, with guide wire), renal artery rupture, puncture site hematomas, and contrast-induced renal failure (1–3). To our knowledge there is no report of type B aortic dissection developing in relation to renal artery angioplasty (1–4). We report a case of a type B aortic dissection that evolved immediately following percutaneous angioplasty of a left renal artery stenosis.

Case Report

A 56-year-old woman with a 20-year history of hypertension was admitted to our hospital with crushing chest pain radiating to her back. The patient's hypertensive medication included Clonidine 0.3 mg every day, Propranolol 20 mg three times a day, Cardizem 30 mg four times a day, and Isordil 20 mg three times a day. The patient's blood pressure on admission was 220/130 mm Hg and she admitted not following her medication prescriptions recently. Although the patient had a long history of stable angina controlled by medication, these symptoms were atypical for her, and the possibility of aortic dissection was suspected. EKG showed normal sinus rhythm at 91 BPM, evidence of left ventricular hypertrophy, and nonspecific T-wave changes, without acute ischemic changes. Hematocrit was 31.5%, BUN 126 mg/dL, creatinine 6.2 mg/dL. Urine analysis showed pH 5, protein 30 mg/dL, glucose 50 mg/dL, red blood cell count 0–2/HPF, whole blood cells 1/HPF.

The patient underwent transesophageal echocardiography, which showed left ventricular hypertrophy, mild aortic root dilatation, but no evidence of aortic dissection (**Fig. 1**). The patient was admitted to the intensive care unit and her blood pressure was brought under control by means of a nitroprusside drip. The patient's chest pain abated. Her creatinine level, which was normal 2 months prior to admission, was now 6.2 mg/dL. A Doppler sonogram of the kidneys showed a normal-sized right kidney (10.2 cm) and normal right renal artery. The left kidney was small (7.4 cm) and there was high velocity flow in the left renal artery, suggesting stenosis. Nuclear renal scan showed diminished flow bilaterally, which could be due to bilateral renal artery stenosis. The patient was sent for angiography.

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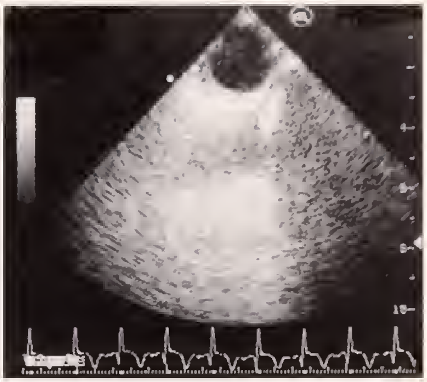
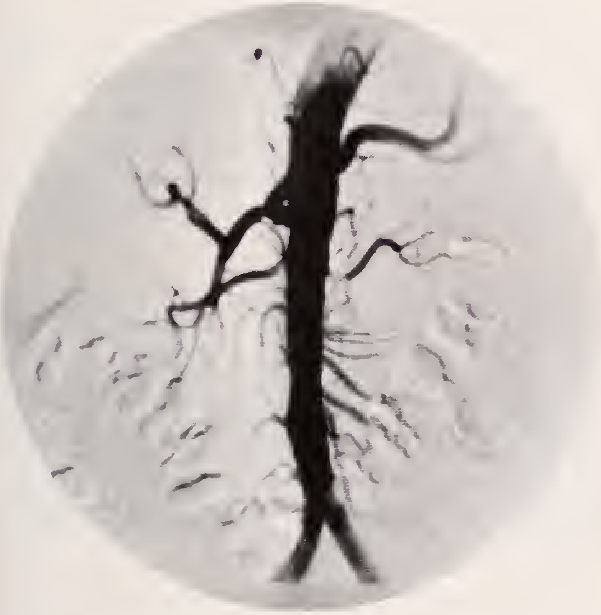


Fig. 1. Transesophageal echocardiogram at level of descending thoracic aorta showing no evidence of dissection.



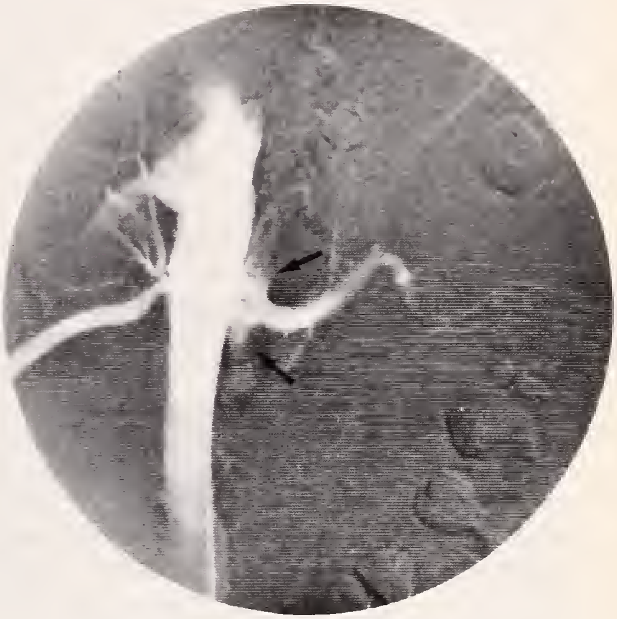


Fig. 2. Left Abdominal aortogram performed prior to angioplasty showing significant left renal artery stenosis and mild right renal artery stenosis. There is no evidence of aortic dissection. **Fig. 3. Right** Aortic flush performed immediately after angioplasty demonstrating false lumen above and below left renal artery (arrows).

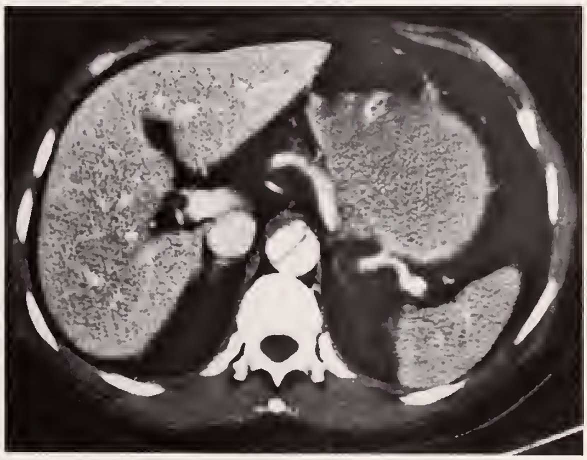


Fig. 4. Representative image from CT scan performed approximately 1 hour after angioplasty showing aortic dissection.

Aortography demonstrated high-grade stenosis of the proximal right renal artery (Fig. 2). There was no gradient across the right-sided lesion. It was decided to dilate the left renal artery stenosis in the hope of improving the patient's hypertension and renal function.

Upon dilating the left renal artery stenosis with a 5-mm-diameter, 2-cm length balloon, the patient began to experience severe back pain. A postangioplasty study was performed with a flush catheter near the left renal artery ostium. The digital arteriogram (Fig. 3) showed narrowing of the infrarenal aortic lumen and filling of a false lumen seen along the left renal artery. A communication (entry point) was seen just superior to the ostium of the newly dilated left renal artery. The patient's blood pressure was 160/100 mm Hg. No pressure gradient remained across the left renal artery.

Because of the findings on the postangioplasty aortogram and the patient's symptoms, she was sent immediately for a dynamic CT scan (Fig. 4) of the chest and abdomen. The CT scan showed a type B aortic dissection starting at the left subclavian artery and extending to the abdominal aorta distal to the left renal artery. The patient was treated conservatively in the intensive care unit with blood pressure control. The patient's renal function failed to improve, and she was placed on long-term hemodialysis. Her blood pressure has been brought under control on oral medications and repeat CT scan showed the aortic dissection to be stable 6 months after the procedure.

Discussion

Aortic dissection is not a reported complication of renal artery angioplasty (1–4). In a recent review of aortic dissection by Cigarroa et al, renal artery angioplasty was not listed as a cause of aortic dissection (5). In our patient, evolution of the aortic dissection clearly was related to dilatation of the renal artery. The dissection was not related to guide-wire or catheter manipulation, since we have evidence on a predilation angiogram that the aortic caliber was normal. In addition, the temporal relationship of the patient's increased back pain after the dilation points to the dilation as an exacerbating event.

This patient had symptoms suggesting aortic dissection prior to the procedure. This led to a transesophageal echocardiogram in the emergency room. This procedure is reported to have a sensitivity of 99% in the detection of aortic dissection (6). The patient may have had medial necrosis of her aorta and was possibly evolving an aortic dissection at the time of that initial episode of back pain. Once the diagnosis of aortic dissection was excluded by the echocardiogram, clinical attention centered on her hypertension. The patient apparently had accelerated hypertension aggravated by noncompliance with medications. The accelerated hypertension and deterioration in her renal function, along with the ultrasound and nuclear medicine studies, raised the suspicion of renal artery stenosis. The patient then underwent the angioplasty, which most likely accelerated the aortic dissection by creating an entry (or reentry) point into a diseased media.

Retrograde type B aortic dissections are rare. Even guide-wire retrograde dissection is easily recognized and rarely extends. It is unlikely that the angioplasty was the sole initiating event in our patient. It is more probable that the dilatation served as an exacerbating event by creating a reentry point into an already diseased media.

Summary

The partial disruption of the arterial wall that occurs with angioplasty may produce an entry point into a vessel with preexisting cystic medial necrosis. At present, there is no clinically reliable method of detecting medial necrosis. One should proceed with caution if angioplasty is indicated and dissection has been recently considered as a clinical possibility.

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Propofol Use in Malignant Hyperthermia:

A Case Report

Gordon Freedman, M.D., Ian H. Sampson, M.D., and Steven Cagen, M.D.

Abstract

We report a case of a patient who developed unexpected intraoperative malignant hyperthermia terminated after discontinuation of volatile agents and kept anesthetized with propofol until the completion of the operation.

Malignant hyperthermia may be triggered by many drugs during anesthesia, including potent inhalational agents and succinylcholine. Propofol has been used successfully in patients with both suspected and proven susceptibility to malignant hyperthermia (1–3). In vitro studies with animals and humans have shown it not to be a triggering agent (4). We report a case of the successful termination of a malignant hyperthermia reaction after discontinuation of volatile agents and conversion to propofol anesthesia.

Case Report

A previously healthy 32-year-old, 110 kg woman was scheduled for left partial thyroidectomy for a slowly enlarging thyroid mass. Preoperative thyroid function tests showed the patient to be euthyroid. She had previously received an uncomplicated general anesthetic for cervical dilatation and curettage, but information regarding exactly which anesthetics were used was unobtainable. Her mother had undergone general anesthesia for a craniotomy, also without complications.

One hour before surgery the patient was sedated with oral diazepam 10 mg. Following a defasciculation dose of curare 3 mg, anesthesia was induced with fentanyl 2 mcg/kg, thiamylal 5 mg/kg, and succinylcholine 1.5 mg/kg. After uneventful tracheal intubation, anesthesia was maintained with N_2O 70%, 0_2 30%, isoflurane 0–1%, fentanyl, and pancuronium. Frozen-section biopsy revealed the mass to be a well-differentiated papillary carcinoma and lymph node dissection was to be included in the procedure.

Approximately 45 minutes into the operation the surgeon noticed tightening of the strap muscles of the neck. Several additional doses of pancuronium failed to facilitate relaxation. Over the next 30 minutes the heart rate increased from 95 to 125 beats per minute; the end tidal CO_2 ($ETCO_2$) increased from 29 to 60 mmHg despite doubling the minute ventilation to 22,000 L/min, and the esophageal temperature increased from 36.9° to 38.4° C. At this time the end tidal concentration of isoflurane was 1.1%. An arterial blood gas examination showed pH 7.24, $PaCO_2$ 57 mmHg, PaO_2 128 mmHg, and base excess -3.4 mEq/L. The surgeon was informed of these changes and asked to finish the operation as soon as possible. The inhalational anesthetics were turned off and 100% O_2 administered. Fentanyl 2.5 mcg/kg and propofol at 0.1 mg/kg per minute were given in intermittent boluses to maintain anesthesia, and the operation was concluded in approximately 45 minutes. With the removal of

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the inhalational agents, $ETCO_2$ decreased to 34 mmHg and both heart rate and temperature decreased over the next 10 minutes to their previous levels. By this time solubilized dantrolene had been made ready, but because of the marked clinical improvement it was decided to keep it in reserve.

After uneventful emergence, she was transferred to the recovery room, where a urine specimen was found to be positive for myoglobin and a blood specimen positive for free serum myoglobin. Serial creatine phosphokinase (CPK) determinations were obtained at 6, 12, and 24 hours. The preoperative CPK had been 307 IU; the initial reading in the recovery room of 6,354 IU peaked to 35,000 IU six hours later and 39,000 at 24 hours, then decreased gradually. Over the next three days the serum calcium levels increased and serum phosphate levels decreased, consistent with rhabdomyolysis. Treatment was instituted with forced saline diuresis, maintaining urine output over 150 mL per hour, and urinary alkalinization was achieved with intravenous sodium bicarbonate to keep the urine pH over 6.5. Blood urea nitrogen and creatinine levels remained normal. Neither the patient nor her family gave any history of myopathy. On the basis of these clinical findings and the blood test results, a diagnosis of malignant hyperthermia was made.

Discussion

Diagnosis of Malignant Hyperthermia. Malignant hyperthermia was first described in 1960 by Denborough and Lovell (5). It is a heritable disorder of skeletal muscle initiated by several triggering agents, resulting in elevated myoplasmic calcium levels. The exact pathophysiology causing malignant hyperthermia is not yet well defined. It is thought to involve an alteration in the function of several proteins in skeletal muscle secondary to elevated levels of certain fatty acids or their metabolites. The chemical properties of the triggering agents that would cause these alterations has not been determined.

Clinical signs of malignant hyperthermia include tachycardia, tachypnea, increased blood pressure, muscle rigidity, and hyperthermia. Laboratory abnormalities include hypercarbia, hyperkalemia, respiratory and metabolic acidosis, hypercalcemia, myoglobinuria, and elevated CPK. Malignant hyperthermia is rare, occurring in approximately 1 in 50,000 anesthetized adults.

Clinically, this patient fits the picture of malignant hyperthermia. She was exposed to the triggering agents, succinylcholine and isoflurane, then intraoperatively developed marked muscle rigidity, tachycardia, hypercarbia, marked respiratory acidosis, and mild metabolic acidosis and hyperthermia. Subsequent laboratory tests revealed a CPK greater than 39,000 IU and myoglobinuria. In patients with masseter muscle rigidity and no history of myopathy, a CPK value greater than 20,000 IU is a highly suggestive indicator of malignant hyperthermia susceptibility (6).

Dantrolene was not given to this patient because of the rapid normalization of vital parameters on discontinuation of the triggering agents. Dantrolene does have side effects such as muscle weakness, nausea, and phlebitis and since the patient's clinical picture was stabilizing, it was decided to closely observe the patient in the recovery room, keeping dantrolene ready if needed. Consultation with the malignant hyperthermia hotline recommended giving dantrolene only if signs of recrudescence occurred, in the form of worsening clinical situation (blood pressure, heart rate, temperature, electrolytes, arterial blood gases) or an increase in CPK levels after the initial peak (in this case the CPK peaked at 39,000 IU and gradually decreased to normal levels).

Thyroid storm was ruled out as a diagnosis by the presence of muscle rigidity, an elevated CPK, and the euthyroid preoperative state of the patient. In a previous report, two cases of intraoperative hyperthyroidism were misdiagnosed as malignant hyperthermia (7). However, in both of these patients the thyroid function tests were significantly elevated.

On several occasions since this event both the patient and her family have been strongly urged to undergo a muscle biopsy for halothane-caffeine testing (patients with malignant hyperthermia have an exaggerated muscle contracture response to these substances), but have not done so to date. This test is important to make a definitive diagnosis of this heritable disease for this patient and her family to prevent any future anesthetic mishaps.

Use of Propofol. Propofol, chemically 2,6-diisopropylphenol, is an intravenous hypnotic agent for induction and maintenance of anesthesia. In vitro studies in which muscle samples from two people and two pigs susceptible to malignant hyperthermia were exposed to propofol, halothane, and caffeine have demonstrated that both halothane and caffeine caused contracture but propofol did not (4). Propofol has been shown not to precipitate malignant hyperthermia in genetically susceptible swine (8, 9). It has also been used successfully in humans with medical histories suggesting potential for malignant hyperthermia (1) and in humans with biopsy-proven malignant hyperthermia (2, 3). The biochemical basis for propofol's nonpredilection to cause malignant hyperthermia has not been elucidated. To our knowledge, this is the first reported case of the use of propofol after the onset of an acute malignant hyperthermia reaction in humans.

Propofol enabled us to stop administering N_2O and to administer 100% O_2 at a time when the patient's oxygen consumption was greatly elevated. In addition to fentanyl for analgesia, propofol facilitated adequate anesthesia, allowing the surgeon to quickly terminate the operation without risk of patient awareness and without exacerbating the acute malignant hyperthermia episode.

Summary

This case illustrates that conversion to propofol anesthesia during an acute episode of malignant hyperthermia may facilitate anesthesia during termination of this potentially lethal complication.

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The Formulary

Isoniazid-Induced Hepatotoxicity

During the past several months, The Mount Sinai Hospital Adverse Drug Reaction Subcommittee has received three reports of isoniazid-induced fulminant hepatic failure, requiring liver transplantation.

The resurgence of tuberculosis has resulted in an increase in the use of isoniazid (INH), along with the other antitubercular medications. Although the incidence of INH-resistant *M. tuberculosis* is reported to be as high as 40% in New York City, INH prophylaxis and treatment are still frequently utilized and it is important that practitioners remain aware of the risks of hepatotoxicity associated with its use.

The introduction of INH in 1952 was a major breakthrough in the treatment of tuberculosis because of its high effectiveness. A few cases of drug-induced jaundice were reported soon after its introduction; however, causality was often attributed to concurrent viral hepatitis or the concomitant use of other hepatotoxic agents.

Since the introduction of INH, clinical hepatitis and elevation of liver function test results in asymptomatic patients taking INH have been reported. About 10% to 20% of patients receiving this drug develop transient mild elevations of SGOT that usually disappear despite continued therapy. These patients should be closely monitored for the possible progression of hepatic necrosis, and therapy should be discontinued in those patients whose transaminase levels exceed three times the normal values. An advisory committee appointed by the Centers for Disease Control concluded that hepatitis occurs in approximately 1 to 10 patients per thousand treated with INH. Fatal hepatotoxicity can occur in approximately 10% of these patients.

The mechanism of INH hepatotoxicity is not completely understood and is felt to resemble a hypersensitivity reaction. Isoniazid hepatitis is characterized by histologic lesions of hepatocellular injury, along with inflammation and necrosis which is clinically indistinguishable from that occurring in viral hepatitis. Although in some cases the presence of eosinophils is prominent, the inflammatory response is primarily mononuclear.

Preventive use of INH has generated some controversy since 1975, although official agencies continue to advocate its use. The following persons are considered to be candidates for preventive therapy:

- those who are PPD positive (5 mm) and infected with HIV, or those at risk for HIV infection who decline HIV testing
- those in close contact (PPD 5 mm) with persons newly diagnosed as having infectious tuberculosis
- recent converters, as indicated by a Mantoux test with an increase 10 mm or greater within a two-year period
- persons with an abnormal chest x-ray that shows fibrotic lesions likely to represent old healed tuberculosis (5 mm)
- persons with medical conditions known to increase the risk of active tuberculosis if infection has occurred (10 mm)
- all PPD-positive (10 mm) persons under 35 years of age

Practitioners may want to consider the risk-benefit of using INH in:

- those patients with suspected drug-resistant tuberculosis
- those at significant risk of INH hepatotoxicity

Risk factors include age greater than 35 years and chronic alcohol use.

Baseline liver function tests, monitoring of liver function during therapy, and approriate patient counseling is recommended for all patients receiving INH, since hepatotoxicity can develop early or late in the course of therapy. The prodrome to jaundice has been characterized by weakness, anorexia, fatigue, diarrhea, and malaise. It is important to inform patients about and monitor them for these symptoms, and to discontinue INH use immediately if these symptoms appear in order to prevent serious hepatotoxicity.

Mount Sinai School of Medicine
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Academic Year 1992/93

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Robert Jioven Valenzuela

Basic Sciences Achievement Award
Laura Ann Karch

Dr. Morris B. Bender Family Award in Clinical Neurology
John Attilio Martignetti, Ph.D.

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The Mount Sinai Journal of Medicine Awards 1992

Ralph Colp Prize

The 1992 Ralph Colp Prize for best surgical paper published in *The Mount Sinai Journal* during the calendar year went to Leigh H. Nadler, MD, and Charles K. McSherry, MD, for their article "Carcinoma of the Gallbladder: Review of the Literature and Report on 56 Cases at the Beth Israel Medical Center" (vol. 59, no. 1). Dr. Nadler and Dr. McSherry are with the Department of Surgery at the Beth Israel Medical Center. The award was established by colleagues and friends of Ralph Colp, distinguished surgeon and for many years chief of surgery at The Mount Sinai Hospital. All *Journal* awards are juried by a committee of five members of the publication's Editorial Board and are presented at the annual Prize Ceremony at the Mount Sinai School of Medicine. The ceremony for the 1992 awards was held on May 18, 1993.

Globus Prize

The 1992 Globus Prize for the best paper with a clinical orientation published in this journal during the calendar year went to the authors of two papers: Clive Rosendorff, MD, PhD, for "Adrenergic Receptors in Hypertension and Heart Failure" (vol. 59, no. 4) and Robert A. Phillips, MD, PhD, for "Pathophysiology and Treatment of Hypertensive Heart Disease" (vol. 59, no. 4). Dr. Rosendorff is Professor and Associate Chairman, Department of Medicine, Mount Sinai School of Medicine (CUNY), Chief, Medical Service, Veterans Affairs Medical Center, Bronx, NY, and Director, The Mount Sinai Hypertension Program. Dr. Phillips is Director, Hypertension Section, Associate Director, Cardiovascular Training Program, Division of Cardiology, Mount Sinai School of Medicine (CUNY). This award honors Joseph H. Globus, founder and first editor-in-chief (1934–1952) of *The Mount Sinai Journal*.

Student Prize

No award was made for the 1992 Student Prize for the best student paper submitted to this journal during the calendar year.

In Memoriam

Margit Freund Klemperer

GABRIEL C. GODMAN, M.D.

WE COMMEMORATE a great lady. For the first time since the inception of this society of alumni and alumnae of the Department of Pathology at Mount Sinai Medical Center, Margit Freund Klemperer is not with us. Many members will recall having seen her, but those among us who came to know her, even a little, will remember her as a woman of exceptional presence, dynamism and warmth. To the few of us who knew her longest, Mitzi was a wise, compassionate, and precious friend whose strength of character, humanitarian impulse, and enormous integrity time had enabled us to appreciate best. The story of her life is inspiring; her wonderful relationship with her husband Paul and her family and friends were conjoined with significant professional achievement and public-spirited action for good causes, and we should here celebrate her success, as we honor her memory.

Margit Freund Klemperer was born in Budapest 93 years ago, the youngest of 13 children of the chief rabbi of that city. Of the closeness, affection, and nurturing warmth of her family life in Budapest she spoke to us often and with feeling; her memories were so richly embellished with anecdotal incident and detail that one was transported in time and place to a far and happy microcosm, forever lost. She spoke especially of her father, whom she adored: indeed, an emancipated and liberal man, yet observant (as was she), he must have deserved her adulation. For, when Mitzi and her sister decided to study medicine, and in another country to boot . . . something unusual and unconventional for young women of that day . . . it was with his approval and support. And so to Zurich they went, and soon after earning the degree, the sisters came to New York to look for work. Mitzi applied at what was then the New York Postgraduate Hospital to the young pathologist, one Paul Klemperer; she got the job at once, and a husband not many months later.

Theirs was an idyllic marriage; a lifelong love affair, perpetuated by a mutual complementarity, support, and sharing which must be rare. Mitzi, with her earthy, practical good sense, was the perfect companion to her gentle, scholarly, somewhat unworldly husband, wholly devoted to science, medicine, and scholarship. Undemanding, he was also woefully underpaid, even by the standards of that day, and Mitzi's professional income not less than her managerial skill in running the household were much needed. Her greatest domestic accomplishment was to have raised and educated two remarkable sons, both of them illustrious: Bill, the eldest, is Hersey Professor of Chemistry at Harvard, a distinguished physics chemist, and a member of the National Academy of Sciences; Martin, who is temperamentally more like Paul, is the much admired Professor of Pediatrics now in Tampa. Whether by genes or nurture, they could hardly be other than men of great character.

Mitzi had to commute all the way to St. Vincent's Hospital in Staten Island, where she served as pathologist, bacteriologist, and clinical chemist. It says something about her that the nuns who ran the hospital, at first suspicious and aloof, became her cordial, lifelong friends, and it was the sister superior who motivated the trip of Paul and Mitzi to Ireland in the 1950s. That trip was one of many journeys that Paul and Mitzi made, always together . . . to Europe, Russia, Israel, Asia, South America . . . alternating between where he had to go and what she wanted to explore. She continued to travel, alone and indomitable, especially to Israel, until the age of 91. But the place that she and Paul loved most of all was the spacious old homestead and farm in Nelson,

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From a eulogy delivered to the alumni and alumnae of the Department of Pathology on June 18, 1992. Address correspondence to the author at 630 West 168th Street, P&S 11-451, New York, NY 10032.

NH that they acquired in the 1940s for a pittance as a ramshackle relic and lovingly built up over the years. They became accepted, integral, beloved members of that old closeknit New England community of flinty Yankees and fixtures of Nelson Village Old Home Day. When Paul died in the mid 1960s, a memorial service was held in the Nelson village church in midwinter, and they brought someone to recite the memorial prayer . . . the Kaddish . . . in Hebrew. The ladies from the village, her neighbors the Tuttles, the Lymans, the Joneses, the Tolmans who loved Mitzi, would visit on summer afternoons bringing gifts from gardens, and be visited in turn, with products of her orchard or bake oven.

From an honorable career in pathology, Mitzi switched (rather radically) to the practice of child psychiatry (in the 1950s), again with signal success, and when she relinquished that practice she returned to pathology, reading biopsies here at Mount Sinai until the age of 83, capable, smart, and respected, an excellent diagnostician, and expert in otorhinolaryngeal and dental pathology.

She was passionately engaged in public and liberal causes, and in the 1950s and 1960s letters signed Margit Freund Klemperer were showered on newspapers, and printed. Remembered with pride, not only by the beneficiaries, are—most of all—the efforts of Paul and Mitzi Klemperer on behalf of emigrés fleeing from Nazi Europe in the 1940s, their staunch protection of Dr. Otani and his family during the shameful anti-Japanese fever here in 1942, their activism against the McCarthy period outrages and on behalf of its victims, their concern for Israel.

Independent, self-reliant, capable to the end, she lived alone in that lovely apartment on 5th Avenue overlooking the park that had been the site of so many warm-hearted, convivial, and educational gatherings, so many cordial conversations. And she kept it just as it was when Paul was alive, always fresh and flowered. It was there that she died, suddenly and unexpectedly, on April 8, 1992, as she would have wished; she is mourned, and celebrated as a still beneficent presence, by those fortunate to have known her.

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Perspectives On Quality Improvement In Health Care

Introduction

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Perspectives On Quality Improvement In Health Care

THIS THEME ISSUE of *The Mount Sinai Journal of Medicine* focuses on quality improvement in health care, a discipline that has undergone significant change during the last several decades. As the nation enters a new era of health care reform, the issues associated with quality in health care will become more important then ever before. Health care providers will increasingly be focusing their efforts on issues of quality juxtaposed with issues of fiscal constraint.

Quality assurance in health care has evolved dramatically, from the traditional outcome-oriented quality monitoring approach to newer process-oriented approaches of total quality management and continuous quality improvement. This pervasive shift in philosophy is most evident in the new standards of the Joint Commission on the Accreditation of Healthcare Organizations (JCAHO), which require all health care institutions to incorporate elements of continuous quality improvement in their quality assurance programs, while not abandoning the more traditional quality assurance and monitoring tools. The articles included in this issue provide an overview of the evolution of quality improvement in health care, and in addition describe diverse quality improvement approaches adopted by many disciplines in the academic health sciences center setting. R. Matz's article provides a useful introduction in its discussion of quality improvement methods and practices.

In his article "Quality, Deming's Principles, and Physicians," L. Teichholz explores the roots of the current revolution in health care quality in concepts developed for manufacturing and other industries and their subsequent application to health care organizations. Additionally, he outlines the development and implementation of continuous quality improvement in health care organizations and its foundation in the tools developed for industry by Deming, Juran, and others. The final section of this article addresses the critical importance of investing physicians in a successful quality improvement process. B. Challan et al.'s article on health care risk management explores one important component of the overall quality assurance function and its current role and scope in health care organizations. As the article indicates, the role of the risk management team will only grow in importance as health care technology continues to evolve, further expanding the ethical issues and appropriate boundaries of medical science.

An additional set of articles, by Jacobson et al., Rehr et al., Ravich et al., and Bradbury et al., describes the historical development and key elements of the quality assurance function in a number of disciplines and clinical areas, including nursing, social work, patient representation, and pharmacy. Each article discusses innovations in quality monitoring, evaluation, and improvement that have been developed at The Mount Sinai Medical Center and, in many cases, have set the example for their respective fields. Weissman et al.'s article on falls prevention provides a specific example of "quality improvement in action," describing the identification of a major, often preventable, patient care problem and the process and systems put in place to reduce its incidence. The article by R. Scheuer on conducting research on human subjects also addresses a specific institutional function in the context of quality assurance, highlighting the importance of applying risk management and quality assurance principles to the functioning of a hospital's institutional review board, the body charged with protecting the rights of research subjects. Finally, the article by Speedling et al. examines the development and application of one specific methodology for measuring and improving upon the quality of patient care in a hospital setting.

The issue closes with a series of book reviews by C. Muller on a variety of topics related to quality of care. The books reviewed cover a broad range of topics, including development of clinical practice guidelines, implementation of continuous quality improvement programs, development of nursing quality assessment programs based on the new JCAHO standards, and needs assessment and outcome measures for primary care.

In addition to the mounting body of literature advocating continuous quality improvement and total quality management, a number of other health care quality trends have emerged, including the growing practice of benchmarking, a growing emphasis on the development of clinical practice guidelines, and increased analysis of data on outcomes. All are being used as a means of promoting both better-quality and more cost-effective health care. Although the articles in this issue do not explicitly address these trends, they are gaining greater prominence in the changing health care environment, particularly as managed care models of health care delivery increasingly dominate the marketplace.

This theme issue is intended to provide the reader with an understanding of how quality assurance has evolved in health care in recent years and the multiplicity of approaches adopted in an academic health sciences center for evaluating and achieving quality patient care. As private sector, state, and federal initiatives continue to emphasize fiscal constraint, health care prices will eventually stabilize. Quality, however measured or defined, will then become the most significant competitive factor in the provision of health care. A commitment to quality in all areas of the academic health sciences center is therefore a strategic imperative for the future.

Special thanks to Jodi Katz, M.Sc., for her editorial assistance with this publication.

A Brief Thesaurus of Quality

ROBERT MATZ, M.D.

QUALITY ASSURANCE doesn't! By this I mean that quality assurance as previously practiced in health care never assured the quality of the care provided.

The approach involved inspection of a final "product"—a medical record or a bad outcome—and made the assumption that deviations from some preconceived outcome were the result of bad providers. In this mode, the quality assurance process attempted to ferret out the bad apples—the "gotcha" approach—and thereby improve overall quality of care. Although this process occasionally resulted in the removal of a few poor practitioners, the ultimate effect on quality of care was minimal. Further, the process engendered a defensive, hostile response from competent health care professionals who were doing their best day in and day out. Much of what was done in the name of quality was paper compliance with outside regulations. It supported the precept that there is nothing so useless as doing something perfectly that doesn't need to be done.

The mechanism of traditional quality assurance was primarily via the isolated bad occurrence, the one-time audit, or the anecdotal incident. Although occasionally necessary and still appropriate, the traditional approach, when used as the sole modality, creates a confrontational atmosphere inimical to real improvement. It especially runs counter to the scientific training and method that has shaped American medicine for the past 70–100 years.

Modern medical care is based on the concept of continuous quality improvement; to the practitioner there is nothing new about it except the name. It avoids reliance on isolated case reports, which, however interesting and educational, may not reflect the bigger picture. In the face of a problem, a hypothesis is generated, data is collected and analyzed, control trials are undertaken, results are subjected to statistical analyses, discussion is undertaken, conclusions are reached, and recommendations for or against certain actions are made. Once these recommendations are implemented, the results are monitored, resulting in the acceptance or rejection or fine-tuning of the hypothesis, as appropriate. This overly simplified analysis of how we have progressed since the Flexner report is familiar to everyone involved in medical care and is now, finally, the approach being applied to the analysis of quality in health care. Unfortunately, the path has been a difficult, frustrating, and painful one, and we have had to relearn our own methodology from industrial models.

A basic tenet of this new paradigm of quality improvement, now being called "total quality management" or "continuous quality improvement," is the need for "doing it with data"—"In God we trust; all others must show us their data." In other words, anecdotes, pontifical pronouncements, and guesses can no longer be the basis for continued practice. In order to understand and achieve quality, the problem must be defined in quantitative, measurable terms.

Another concept which has evolved is "doing the right thing right the first time, every time." This encapsulates the entire purpose of continuous quality improvement, and every word of the statement is critical. It means not waiting until the end of the process to "inspect" the product and then reject it if it is not right, but rather building quality into the process and product from the very beginning. Quality assurance by inspection is wasteful and costly and dangerous.

The new paradigm of continuous quality improvement assumes that everyone comes to work

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every day to do the best job of which they are capable, given their education, available resources, the current system of doing things, and the material they have to work with. With this in mind, the approach to improving the outcome is to look at the system or process and attempt to continuously improve its elements, thereby enabling everyone to do the right thing in the right way the first time, every time.

Another valuable precept is that processes or systems are never perfect. They may statistically approach perfection, but all processes fluctuate around some statistical mean, and tinkering with a process which is "in control" or working may be inappropriate. In order to look at these systems or processes in a meaningful way, however, we must understand the process and collect sufficient data to enable us to analyze it with a reasonable degree of statistical validity. There will always be some variation around the mean, and this may or may not warrant our attention. The point is that establishing a threshold for a process and then not looking at it if the threshold is not violated is no longer acceptable. If we meet or even exceed our "threshold," the next step in continuous quality improvement is the "benchmark"—a point of reference which serves as a standard by which the process may be measured. This is conceptually the high water mark—the best in the business—for which we all strive. And if we get there, we should try to exceed it. That is quality improvement.

But beware; "Perfection is a city in Russia and nobody wants to live there." There may come a point in the improvement process when the next step is just too costly, too difficult, or too unimportant to warrant taking it. It is the journey toward perfection which is important for most processes, the step-by-step continuous process of measuring, analyzing, and monitoring, and—when necessary—changing to reach and exceed the benchmark. As David Kearns, chief executive officer of Xerox, has so aptly put it, "In the race for quality there is no finish line."

How should we define "quality"? Quality is what our customers expect of us, and the only way to know what they expect is to ask them. Why do I say "customers" instead of patients? Because whether we are physicians, nurses, social workers, or technicians, we all have many individuals (not just patients) who expect something of us in this complex process called health care. The physicians' orders must be clear and timely in order for the nurse to pick them up and request transport to take the patient to x-ray. At every step in this process we each are attempting to satisfy—yes—"customers." The only way to know whether we are meeting their expectations is to ask; patient satisfaction surveys and interdisciplinary quality improvement groups begin this structured analysis. Only by this multidisciplinary process can we define what quality is. Quality is never accidental. It is the result of thoughtful design. One definition which I like is, "Quality is meeting or exceeding customers' expectations 100% of the time."

How can we evaluate such a complex system, find its flaws, and modify and improve it? By asking the people who actually perform these activities what they do, how they see the process, how they would measure it, and what they think could be done to improve it. Then we must permit them, within limits, to act. This requires a willingness on the part of management to listen to employees—a process that can be threatening to middle management, though it need not be. Most important, it requires a commitment from the top of the organization such that the process of quality improvement will become a part of the ethic of the institution, that employees will be empowered to seek processes that need improvement and, where appropriate, to implement the recommended actions. It means an organizational commitment to quality improvement as job one.

This is a top-to-bottom approach which takes time and resources—no quick fixes, no one-time audits, but a continuous, open-ended process of looking and improving. In most instances where continuous quality improvement has been incorporated into the institutional structure it has, in the long run, been cost effective.

The papers in this symposium reflect the spectrum of the changing face of how quality is looked at, measured, and ultimately improved in the hospital setting. They cover many disciplines in the health care process. This is only a beginning. As evidenced by the high quality and broad range of contributions, the future looks promising for the application of these new tools in the quest for continual improvement.

Quality, Deming's Principles, and Physicians

Louis Evan Teichholz, M.D.

Quality

In the 1980s, driven by standards from the Joint Commission on Accreditation of Healthcare Organizations (JCAHO) and by external regulatory agencies in the various states, the concept of quality assurance became an important concern for hospitals in the search for quality. The quality assurance approach in the health care field has concentrated on analysis of structure, process, and outcome. Much of the emphasis has been on outcome—what happens to patients. This concept of quality assurance is based on examination of poor outcomes and to a large extent on the "bad apple" theory, which implies that the problem lies in the individual and that people must be made to care. The emphasis has been on quality problems as faults of people rather than of the process itself (1). This quality assurance process has been described as static (2), adversarial, and punitive, thus fostering a "we" versus "they" attitude. It has been reactive rather than proactive and based on the concept that quality can be improved by inspection and overseeing rather than by changing the process (3). Separate departmental quality assurance staffs have been developed, which can undermine institutional teamwork (4), and in many hospitals the quality assurance department has been perceived as a policeman. Most important, most physicians have lacked interest and scanted involvement in this important process because of the adversarial stance and because physicians are in many cases outside the process (5).

Despite much experience with this approach, whether it has improved the quality of medical care in any major way is not clear. Certainly no evidence exists of increased patient satisfaction; and no significant improvement appears to have occurred in another dimension of improvement, patients injured in hospitals: a California study conducted in the 1970s found that 0.82% of 20,000 hospital patients showed some disability believed to be caused by negligence (6), and a Harvard study conducted in 1984 of 30,195 patients in New York State found that 1% had meaningful disability deemed to be caused by negligence (7).

Quality is the end result of a complex interaction of people and support systems (5). The current process has not gone much beyond superficial problem analysis and finger-pointing. However, in the 1990s the focus has started to change. Although outside regulatory agencies are still applying pressure on quality assurance and reporting of poor outcomes and complications, we are entering a new era in which, clearly, the way to improve quality is to improve the process itself. The role of the quality assurance department must change from being a cop to being a "coach" (4), and quality must be totally integrated within the hospital management system.

The new revolution is based on the pioneering work on quality in industry by Deming, Juran, and others, initially introduced in Japan and now being applied to American industry (8–15). Berwick (3, 16) and others (2, 17–20) have applied these industrial concepts to the health care setting, and the term "continuous quality improvement" (CQI) has emerged. Another term usually used synonymously with CQI is "total quality management" (TQM). The focus in CQI is the prospective analysis of statistical data and trends, not—as with the older concept—retrospective review of individual cases with poor outcomes. The emphasis now is on finding common denomina-

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tors and asking what the overall process is and whether it can be improved, not on what went wrong in any individual case.

The Hospital Corporation of America has applied Deming techniques to hospital organization (10) and various hospitals—the University of Michigan hospital (21) is one—have described their experiences with this technique (20–26). The applications of CQI to improving physician care have recently been reviewed (27).

Most importantly, the National Demonstration Project on Quality Improvement and Health Care was developed in September 1987 to answer the question, "Can the tools of modern quality improvement, with which other industries have achieved breakthroughs in performance, help in health care as well?" (28). This National Demonstration Project "achieved the goal of showing that the concepts and tools in industrial quality improvement can be used to improve the quality of processes in the health care industry. . . . The familiar tools of industrial quality improvement . . . [have been] successfully applied to a wide variety of health care processes" (28).

The process of continuous quality improvement encompasses a multiplicity of concepts, including statistical quality control and a new management philosophy (2, 3, 18, 20, 25, 28). The JCAHO has adopted CQI as an important new concept and is revising its standards and review to reflect the new principles (29). A major goal is to modify most standards to reflect the basic concepts of CQI by 1994 (30). In fact, a recent poll of hospital chief executive officers indicated that almost 60% are now implementing a CQI/TQM program and, of those without a program, 75% were planning to start one within the next year (31). The American Hospital Association has recently published three books to help hospitals and physicians turn theory into practice (32–34).

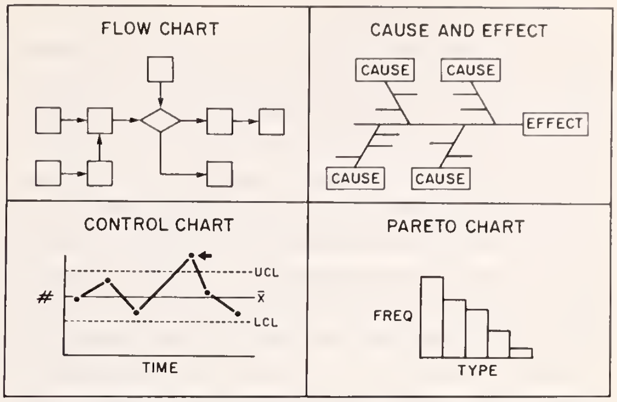

Fig. 1. Four important graphic tools for statistical control processes: flow chart showing each step in a process; cause-and-effect or Ishikhawa diagram; control chart to analyze variation over time of any parameter; Pareto bar chart delineating frequency of each factor contributing to an effect. $\bar{X}$, mean; UCL, upper control limit; LCL, lower control limit; arrow, data point outside control limits.

Deming's Principles

W. Edwards Deming was born on October 14, 1900 and grew up on a Cody, Wyoming homestead. He received an undergraduate degree from the University of Wyoming in 1917, a master's degree in mathematics from the University of Colorado, and a Ph.D. in physics from Yale University. He initially worked at the Hawthorne plant of Western Electric, and joined the U.S. Department of Agriculture in 1927. During subsequent years, he was introduced to Dr. Walter Shewhart at Bell Laboratories and became involved in learning and understanding statistical control methods. He also studied statistics with Dr. Ronald Fisher. Because of his expertise in statistical control and sampling methods, he was enlisted to develop statistical methods for the 1940 census and, during the war years, he taught statistical methods and quality control. In 1947 he was again enlisted, this time by the Supreme Command Allied Powers, to prepare for the 1951 Japanese census, and thus began his long association with Japanese industry.

Deming taught the Japanese his methods of statistical control and quality improvement and became widely known in Japan, revolutionizing their quality process in industry. However, his methods and philosophy were not well known in the United States, nor was there any widespread application in American industry until after a 1980 NBC television special about his techniques in Japan. His book, *Out of the Crisis* (35), published in 1986, served as the foundation for the current revolution. Deming proposed and discussed applications of his methods to the health care setting in that book. Public discussion of application of his principles to health care began about two years later, in 1988, and has gathered steam since (20, 36–39).

Statistical Methods. The major contribution of Deming is the concept of statistical control processes and the application of statistical theory and methods to the improvement of quality. In addition, in *Out of the Crisis,* he proposed 14 points which have broad implications for industry in general and health care in particular, both for overall organizational structure and goals and for quality improvement itself.

Statistical quality control is a tool for understanding a process, determining whether changes need to be made, and following the effects of such changes. It is based on the concept that performance differences may be in large part related to chance variation—random processes—and one must look for those processes that are "out of control." Thus, a statistical theory of random variation was built into a theory of quality management. Inherent in the concept is the need for more information and for theoretically grounded tools to answer questions (3, 36, 38, 39). The modern approach to quality must therefore be thoroughly grounded in both the scientific method and in statistical theory.

Tools for Statistical Control. The National Demonstration Project successfully demonstrated the application of these principles. The purpose of the quality improvement effort is to eliminate unnecessary variation. In order to accomplish this, various graphic approaches have been proposed and discussed (2, 5, 9, 28, 40); the major graphic tools are demonstrated in **Fig. 1.**

The first tool is a flow chart, which represents steps in any process, thus allowing a clear and logical understanding of each individual step. It allows one to zero in at various stages of a process in terms of quality, similar to a computer flow diagram.

A second tool is the cause-and-effect or Ishikhawa diagram, sometimes called a fishbone diagram because of its shape. In this diagram, the effect is the head of the fish and the various potential causes are the bones along the spine. It is helpful for identifying, displaying, and characterizing various causes that can lead to a given effect. It represents relationships and subprocesses, and thus is an aid to understanding the complexity of problems and determining objectively all the factors that might cause a given effect. Examination of this diagram in conjunction with the flow chart allows one to generate hypotheses about a given problem in quality. Once these hypotheses are generated, one can attempt improvements.

Two additional diagrams, the control chart and the Pareto bar chart, display information and data so that conclusions can be readily drawn. The control chart, developed in the 1920s by Walter Shewhart and adapted by Deming, is at the center of this entire process. The chart is based on the concept that some variation is inherent in any process, and that one must therefore plot the variation over time of any given parameter—for example, the complication rate in a cardiac catheterization laboratory. These statistical control charts can demonstrate changes or trends as alerts that the process may be "out of control" and requires further investigation.

It is important to distinguish inherent or random variation in any parameter from variation which is real and significant and thus needs to be addressed. Inherent variation is called "common cause variation" and abnormal variation, when the process is "out of control," is called "special cause variation." The control chart enables one to determine whether the process is stable and predictable or contains aberrations. To properly use these charts, the "normal" degree of variation must be determined so as to see when the normal limits are exceeded. Thus, upper and lower control limits, which can be calculated using statistical procedures such as standard deviations or can be based on information from other studies, must be established. The use of control charts is helpful in the formulating and more important in the testing of hypotheses to determine if changes in the process truly affect the data. When there are special causes, it is important to change the process itself. However, one must be careful of what has been termed "tampering": treating common cause variation as if it were an important problem for quality and overreacting. The best medicine against tampering is the use of the control chart.

The Pareto bar chart arranges various factors contributing to overall effects in the order of their decreasing frequency. It is named for the economist who stated that relatively few citizens held most of the wealth in an economic system, an idea applied to quality control by Juran as the Pareto principle: "Whenever a number of individual factors contribute to some overall effect, relatively few of those items account for the bulk of the effect" (28). These diagrams allow one to clearly see the major confounding factors that enter into a process that has a potential problem in quality.

A key point is that the methods described above have been successful both in industry and in applications to quality in the health care field. But, in Deming's words, "Industry in America (as Shewhart said) needs thousands of statistical-minded engineers, chemists, physicists, Doctors of Medicine, purchasing agents, managers" (35). Deming's methods must be applied to the quality process if we are to succeed; however, blind application of statistics to the process will not in itself contribute to improved quality. A significant change in overall goals, philosophy, and direction of the total organization is vital to success; health care institutions must "organize for quality" (3).

Deming produced a total framework on which to build this quality endeavor, his 14 points (35), widely quoted in many settings and applied and adopted in industry and—of particular interest here—in health care settings, especially to the quality process, as discussed below.

Point 1: Create constancy of purpose for improvement of product and service. Constancy of purpose is extremely important not only for quality but for the entire organizational structure and goals of the hospital. Goals must be defined, and appropriate resources put into place to accomplish these goals. Long-term rather than short-term, put-out-the-fire solutions must be emphasized. To accomplish the long-term goals, innovation and rethinking are required. In terms of the quality process, one must not look for quick fixes, but rather recognize and instil quality as central to the organization. True commitment on all levels is essential for quality improvement; this consistency of purpose implies not just filling out forms for reporting agencies or preparing for periodic Joint Commission visits, but rather the adoption of the other Deming principles in order to change the system. Deming urged, "Translate this constancy of purpose into service to patients and the community.... The Board of Directors must hold on to the purpose" (35).

Point 2: Adopt the new philosophy. The new approach to management and to quality improvement must be not just a technique but a total philosophy. The organization must understand that the best way to improve quality is to improve the process and do things right the first time. Both individual and corporate attitudes must change, and the new philosophy must pervade the entire organization, including both management and physicians. The organization must truly believe in quality. If this is not achieved, the concepts of continuous quality improvement and the improvement of the process will fail. The other points give us insight into what can be done to aid in the adoption and acceptance of this new philosophy.

Point 3: Cease dependence on inspection to achieve quality. A major philosophical concept should guide the change from quality assurance to continuous quality improvement. Deming said that the old way was to "inspect bad quality out" and the new way was to "build new quality in" (35). True quality is derived not from inspection but from improvement of the entire process. The current quality assurance system is unfortunately the ultimate inspection system, with reviews and audits and, for the most part, examination of bad outcomes and affixing of blame. However, inspection comes too late in the process of health care to improve quality. When a complication of a procedure has occurred, a medication error has been made, or a patient has already fallen and broken his or her hip, it is too late. The most effective inspection process will not undo the damage. Patients deserve better. In many cases, a proper assessment of the process before the event could have led to improvement in the process and avoidance of a poor outcome. Continuous quality improvement attempts to accomplish this. By looking prospectively at the process, using appropriate statistical techniques and capturing proper information from all patient encounters, not just those with poor outcome, one can appropriately review not just the individuals involved but the process itself.

Deming never suggested the abolition of inspection but rather emphasized not depending on inspection. Inspection should be an option rather than the rule. In fact, one needs inspection to monitor how one is doing, especially when upgrading quality. One can use control charts (see above) to pick out special areas for inspection. The key is that the standard method for improvement is not based on this inspection process. However, until regulatory agencies are also aware of and adopt the same philosophy, the filling out of reports of poor outcomes will unfortunately still be with us. One challenge for the future is how to incorporate this appropriately in the continuous quality improvement process.

Point 4: End the practice of awarding business on the basis of price tag alone. Deming amplifies point 4 in regard to trying to use single source vendors. He sees vendors as partners in a long-term relationship that should lead to higher quality. How does this apply in the health care setting? First, it applies directly to conducting the business of the hospital in the Purchasing Department. A hospital is a business organization, just as an industrial organization is, and similar management principles apply. The most successful industries have learned that the total cost of supplying a service or producing a product is not just purchase price, whether of raw materials or other necessities. The hospital must not buy medicines or supplies purely on the basis of price. This principle also applies to decisions about personnel levels. Although reducing personnel giving direct patient care in various areas may initially appear to reduce cost, the overall future costs resulting from quality problems may be quite dramatic. One must not look solely at the current price tag but also at long-term costs for both equipment and personnel. Deming is succinct: "Price has no meaning without a measure of the quality being purchased" (35).

Point 5: Improve constantly and forever every process for planning, production, and service to improve quality. Point 5 follows from Deming's points 1, 2, and 10 and is the essence of continuous quality improvement. The process must not be static. An organization, and the quality of its products, must be constantly undergoing change brought about by the appropriate application of statistical control principles and of continuing evaluation. The use of statistical control methods is central to improvement. In addition, quality is not a one-time effort. The quality process must not be used to put out fires, but rather to change overall management and processes. One must not set a target and then, when it is reached, stop and feel that the process is complete. Reassessments and attempts at improvement of performance must constantly recur. Even if a complication rate for a procedure is "within local or national standards," we could still further improve our performance and the quality of care to our patients.

How do we accomplish this? By using statistical methods of quality control; however, they must be applied using the conceptual framework of the Deming-Shewhart Plan, Do, Check, Act (PDCA) cycle (9, 19, 35) **(Fig. 2)**. The first step is to plan, beginning by studying a given process in detail, using the scientific and statistical methods. For this study one must know what data are available and what data need to be obtained. By the use of flow diagrams and cause and effect charts, one should determine what possible changes might improve the process, then create a plan for making a change and a clear method for observation of the change to determine its effects on the total process.

In the second step, the "do" portion, a single change is made on a small scale. In the third step, the "check" phase, observations are made and data obtained on the influence of the change on the various effects. The fourth phase is to act on the observations—appropriately examining the data, testing hypotheses, and coming to conclusions.

Once it has been determined what one has learned from the change or intervention, then one must decide whether it was successful and to what extent. This information should then be used to move to a newer cycle, either to institute this change more widely and reexamine its effects, or to modify the plan and examine an additional area for improvement of the same process. Thus by a continuing process we slowly continue to improve on the quality of our medical care by climbing to successive cycles, that is, quality improvement that is truly continuous. To remove any connotations of checking, blocking, or reining in this never-ending process, which aims at a complete look, Deming recently substituted the word "study" for the original word "check" in the third step of the PDCA cycle, which thus is now known as the PDSA cycle (13, 14).

Point 6: Institute training on the job. Each individual in the organization must have the appropriate training to know what his or her job is and how to improve performance. Training has always been part of the nursing process. We must also appropriately train technicians and other members of the health care team, including physicians. Credentialing of house officers should not be by the "see one, do one, teach one" process, but by formal plan with formal evaluation. All members of the organization must be trained in the quality process, including at least an introduction to the concept of control mechanisms. Supervisors must be seen as facilitators and must appreciate that individuals learn in different ways, requiring innovation in training. However, unless universal training is in the concepts and methods for improved quality, the entire process is doomed to fail.

Point 7: Institute leadership. Deming has said that "the job of management is not supervision, but leadership" (35). Leadership must support a pervasive climate of concern for quality and must maintain and support Deming's principles, especially constancy of purpose and adopting the new philosophy. All must work together on the quality process. Human error does occur; however, few workers go to work intending to perform their job poorly. Managers should be like coaches, helping their workers in the continuous quality improvement process and in striving for excellence.

Point 8: Drive out fear. Driving out fear is vital to accomplish the other goals. People must feel secure in their position and must not be afraid of making suggestions out of fear of how their supervisors may react. If people are afraid to ask questions when they do not understand, the same problems will be repeated over and over. Workers must be given the benefit of the doubt and systemic rather than individual problems must be emphasized.

Fear is built into our health care system. Nurses are usually afraid to question doctors. Physicians fear the consequences of risk alerts or reports to regulatory agencies. In addition, the reporting process has an adversarial tone: nurses file risk alerts and are "responsible" for incident reporting, while physicians sometimes have the perception that such reports constitute "telling on physicians." Another fear of the quality assurance process is of severe disciplinary actions, when the fault lies primarily with the system. We must adopt a new attitude removing fear from the quality process to evince full cooperation and assistance from all members of the health care team.

Point 9: Break down barriers between staff areas. No communication can take place if fear is endemic. Unfortunately, the hospital medical system entails a dichotomy between management and doctors, between doctors and nurses, and even between the quality assurance and the risk management departments. Yet teamwork between departments, not competition, is a must, because the entire quality process is full of interconnected processes in which individuals are both providers and consumers. We must develop a total integrated approach to risk management and quality improvement, in which all staff work with common data for common goals. For example, in patient areas the quality process must be a combined effort of nurses and physicians. Reporting systems should not be dual or multiple, but totally integrated. Deming has said: "We must break down the class distinctions between types of workers within the organization—physicians, non-physicians, clinical providers versus nonclinical providers, physician to physician" (35).

Point 10: Eliminate slogans, exhortations, and targets for the work force. Slogans may be catchy but are no substitute for a total philosophy to develop quality improvement in an organization. Slogans usually imply that "bad apples" or noncaring people need to be exhorted. Nor will slogans used as targets improve quality. However, slogans may have a limited role in fostering group identification and teamwork, if the slogans really come from workers and are part of the total institutional philosophy and practice.

Point 11: Eliminate numerical quotas for the work force and numerical goals for managers. According to Deming, quotas in industry, especially for quality, are counterproductive. Quality, not quantity, is important. However, improvement of quality can lead to increased efficiency and therefore to increased quantity as well. If performance differences are largely due to chance, setting targets will not alter the process. In addition, numerical targets can be manipulated—as in "If you want to hit the target, shoot first and then call what you hit the target." Using targets, whether they be 85%, 90%, or 95% compliance with a given standard, is alien to the concept of continuous quality improvement. Even if a process is deemed good, it can be made better. We should not work for numerical goals but constantly strive to improve ourselves, the process, and the organization. Deming has stated: "A quota is a fortress against improvement of quality and productivity. I have yet to see a quota that includes any trace of a system by which to help anyone do a better job. A quota is totally incompatible with never-ending improvement" (35).

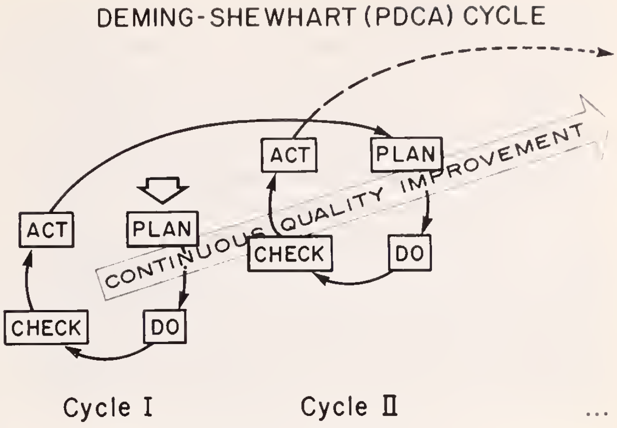

Fig. 2. Deming–Shewhart cycle: Plan (P), Do (D), Check (C), Act (A).

Point 12: Remove barriers that rob people of the pride of workmanship, including annual rating or merit systems. Perhaps one of Deming's most controversial principles is that an annual rating and merit system works against the other general principles because it tends to reward individual, not group, effort, thus undermining teamwork, and is based on the idea that individuals rather than systems are the root of problems. He feels emphasis should be on the sense of a job well done and the pride of participating in improving the system. He also believes that merit awards are not necessary if all people are trying hard to do their best and know what is expected of them. Remember that even in ideal circumstances, with ideal productivity and ideal quality, half the individuals in a given area will be performing below average and half above average. Instead of concentrating on merit ratings and their relation to salaries, the entire work force must be instilled with the idea that quality is a proper goal and that people should take pride in the performance of their job. This may be difficult, but it is extremely important if the quality improvement process is to succeed.

Point 13: Institute a vigorous program of education and self improvement. Quality begins and ends with education. Continued learning for all in the hospital setting must be the rule. People should be educated in various ways to improve their job skills and to advance within the organization. Unfortunately, education and training tend to disappear early with hospital budget cuts, although workers educated in relation to their job will be more likely to improve job performance. Equally important, the whole organization—at the lowest as well as the highest levels—must be educated in the concepts of quality and, where appropriate, in the scientific methods and statistical techniques involved. Everyone must clearly understand his or her own role in contributing to the improvement of quality in the organization.

Point 14: Put everyone in the company to work to accomplish this transformation. This point encapsulates the previous points. Everyone in the organization must understand the importance of quality and must agree on the new philosophy. The major technique for accomplishing this transformation is not only the philosophical adoption of these principles but the application of statistical methods and the Deming-Shewhart PDCA cycle to continuous quality improvement.

The Role of Physicians

One of the significant reasons for the failure of the current quality assurance process is the general lack of physician interest and involvement. Several reasons for this have been recounted above. For many physicians, "quality" is equated with "trouble." Even the peer review process primarily examines single episodes of poor outcome as deviations outside the system. The premise is that quality can be improved by singling out those physicians involved in the care of patients with poor outcomes and assuming that the physicians have not provided an acceptable level of care (27).

Physicians must be part of the solution rather than a significant part of the problem. Juran has described the problem of an "immune reaction" to the quality process; physicians may prove to be "killer lymphocytes" in opposing quality processes in health care organizations (5). To succeed, continuous quality improvement requires the participation of physicians on all levels, as Berwick notes: "quality improvement has little chance of success in health care organizations without the understanding and participation, and in many cases, the leadership of individual doctors" (3).

Is it possible for physicians to become actively involved in the process? The National Demonstration Project yields some insight. Although the Project found incorporating physicians into the planning and team processes was initially difficult, once physicians became involved they were active contributors (28), in part due to their familiarity with the use of scientific methods at the heart of the statistical control process. The Project concludes: "In fact, barriers to physician involvement may turn out to be the most important single issue impeding the success of quality improvement in medical care" (28).

A major method for accomplishing physician involvement is by education, at all levels. Medical schools must add to their training curriculum an understanding of the concepts of continuous quality improvement as well as an introduction to statistical control methods and the application of scientific and statistical methods not only to clinical research and patient care but also to the quality process. Since a large portion of acute care is provided by housestaff, especially in teaching institutions, all housestaff need an educational program that crosses departmental boundaries. However, the most important group to be trained are the attending physicians themselves; they are the primary providers of health care both inside and outside the hospital. Although the emphasis has been on quality issues inside the hospital, these principles and concepts must be adopted as part of an overall philosophy and applied to out-of-hospital practice as well. In addition, the Board of Trustees of the institution must also be educated and have a total commitment to this process; this may pose less of a challenge, since many trustees may already be familiar with the industrial applications of the principles of Deming and others. The key, however, to the success of continuous quality improvement rests in the hands of the chairpersons of the hospital and medical school departments and, in academic centers, in the dean and his or her office as well. They must actively embrace the concept, be its champions, and actively lead physicians and faculty. This will require the allocation of adequate resources for both education and implementation and will entail initial costs, space, and personnel. However, we cannot afford not to make this investment in quality, which will have tremendous payoffs in the future.

Furthermore, institutions must break down dichotomies between the physician hierarchy, the hospital administration hierarchy, and in many cases the nursing hierarchy. To be successful in involving physicians, health care organizations will have to remove critical barriers and the fear of surveillance. All members of the team must work together nonadversarially to improve the quality of hospital services and patient care. Quality improvement requires "candid, non-retributional self-examination" (27).

To begin enlisting physicians—and they must enter the process at an early stage—unrealistic expectations of overnight achievement must be avoided. After the development of a true institutional commitment, a few clearly defined projects are necessary to involve physicians and to demonstrate the usefulness of the technique. If one starts with small steps and uses statistical control methods and the Deming principles, including repeated Deming-Shewhart PDCA cycles (Fig. 2), in my opinion the superiority of the approach will quickly become evident. Quality must be improved in small steps, and initial successes in clearly circumscribed areas will serve to convince more and more health care providers of the utility of the process. Actively involving physicians will not be easy, but the results of the National Demonstration Project show that it can be done. Physicians must learn to see how their own interests can be served by participation and how their own future is also connected to the health care organization in which care is given; the process must be actively physician driven. This is the central issue for the future success of continuous quality improvement.

Conclusions

The words "crisis" and "opportunity" are represented by the same Chinese ideograph. The current crisis of quality in health care in America contains the opportunity to go forward and solve many of the problems that exist. Continuous quality improvement must not be just a slogan. The entire organizational structure, including not only administrative leadership but also the community of physicians, must be committed to it. Japanese industry and subsequently American industry have embraced many of Deming's concepts. It is clearly time for the health care industry to do the same. However, these techniques are not a quick fix for all the ills and problems of American medicine. We must also recognize that "quality issues are larger than any particular spokesperson and supersede passing fads, but to keep them from becoming cultish, the ideas rather than the guru must be emphasized" (23).

The techniques outlined in this paper are a starting point. They will give us the necessary tools for the future improvement of the quality of care. In addition, this philosophy should improve the organization in other ways. The costs of poor quality—inefficiency, reworking, excess lengths of stay, malpractice exposure, and litigation—are among the major problems in the health care system. At the same time, fully estimating the effects of quality improvement on health care costs is impossible. The industrial quality consultants in the National Demonstration Project commented that the problems of waste, reworking, and variation were greater in the health care industry than in many other industries. They estimated that the cost of poor quality was significant; in fact, several suggested that these costs could approach almost half of the total health care bill (28).

If the health-care industry is to survive its current crisis and capitalize on the new opportunities, it must adopt the philosophy and methods of continuous quality improvement. David Garvin of the Harvard Business School has concluded (41):

> The experience of several participants suggests that quality improvement, far from being a diversion, leads directly to greater efficiency and cost reduction. Indeed, if, as seems increasingly likely, the basis for competition in health care shifts from a pure price basis to some combination of price, quality of service, and quality of care, then the issue of quality will be fundamental to the survival of many health care organizations. Far from being an interesting, but tangential, activity, there is reason to believe that quality is likely to become an important basis for competing in health care over the next decade.

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Risk Management in Health Care:

Where Did It Come From and Where Is It Going?

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Abstract

This article reviews some of the historical developments contributing to the evolution of risk management and its current role in health care. The scope of activities and concerns that today's health care risk managers address and the need for involvement by the entire health care team are discussed.

WHEN A PHYSICIAN who is innocently going about the daily business of seeing patients at the office is told the hospital risk manager is on the phone, he or she knows, even before picking up the phone, that there is a problem. Only a few years ago, many physicians had never even heard of risk management. Now it is hard to avoid the constant influx of bulletins, newsletters, and seminar notices hawking the latest in how one may end up in court. Where did this relative upstart of a health care discipline come from, and where is it going?

Historical Background

Until the 1970s, the health care field was less affected by the costs of liability losses than many other industries in this country. Furthermore, until then, most businesses were more concerned about property losses than liability losses. The liability revolution had not yet struck. For health care, the patient rights movement of that decade abruptly changed all that. Patients no longer wanted to be "done to," but instead demanded to participate, to be informed before giving consent to treatment, and to sue for damages when they believed negligent care had been provided.

The courts supported this new patient activism, awarding huge financial compensation for injuries in medical malpractice suits. This fundamental change in the attitude of patients and the courts, along with shifting public policy, tore through the buffers of doctor-patient trust and professional insularity to make hospitals and doctors targets for unprecedented liability losses.

At the same time, hospitals in many parts of the country were losing the charitable immunity from civil suits that had long protected their operating budgets and other assets. Not-for-profit institutions became as vulnerable to losses from lawsuits as for-profits. Furthermore, plaintiffs' attorneys were becoming increasingly skillful at trying medical malpractice cases, causing both hospitals and physicians to fear them more. Many industries, including health care, lobbied state legislatures for tort reforms to help stem the overwhelming losses from liability claims.

The 1980s brought cost containment initiatives and more (and more) governmental regulations. Political scrutiny was joined by increasingly aggressive media coverage; new, exotic medical technologies and medical mishaps provided plenty of grist for the reporter's mill. With health care delivery now on the priority list of national problems, the field will continue to operate under the public's gaze. The quest for civil tort reforms will continue as well, because of ever-expanding theories of liability.

In the last two decades, the burden of liability losses, as well as compliance with federal and state statutes, has become an increasing drain on financial resources used for patient care, research, investment in new equipment, and other

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improvements in delivering medical service. To stop this liability drain, the health industry began to allocate more resources to risk management in an attempt to control risks more effectively while improving the quality of care.

Until the late 1970s, large hospitals had at most an insurance manager who purchased the requisite insurance coverage and tracked the sources of some insurance losses. When a hospital realized it could no longer afford to just "roll with the punches," and the public continued to demand more oversight, a risk manager was hired and charged with gaining control over liability losses through prevention and quality improvement. Smaller hospitals assigned risk management as a part-time function to an administrator.

Evolution of Risk Management

To health professionals who are schooled in keeping patient information private, the whole process of risk management can be uncomfortably candid—not to mention suspiciously trendy. However, risk management is not a recent phenomenon and has its roots in insurance. Risk management has had a well-established role in other industries for hundreds of years and in medicine for at least a century. Gathering and analyzing information, while safeguarding it from improper disclosure, is essential to managing risks and achieving loss reduction.

Since the dawn of the industrial age, people have been negotiating ways of protecting business owners from avoidable losses. The roots of insurance can be traced back 300 years, to the era of hazardous overseas trade, when Lloyd's of London first gathered small sums of money from ship owners to cover the cost of lost cargo.

At that time, "risk management" efforts were focused on financial losses from sunken cargo. Over time, both insurers and business owners perceived the benefit of prevention through fire safety, machine safety, protection from natural perils, ad infinitum. In addition to the intrinsic worth of human life and health, the increasingly sophisticated skills possessed by workers came to be viewed as yet another kind of potential loss. A loosely organized, often totally unorganized array of many types of insurance and mandatory and voluntary loss prevention mechanisms developed to protect individuals and organizations from harm and, ultimately, financial loss. Not until the industrial revolution, when work-related injuries grew exponentially, did personal injury liability claims become a major issue; management of the risk of loss eventually became integral to determining an organization's viability and potential for growth.

Risk management now covers the gamut of industrial concerns from plant safety to product reliability. As American businesses become more complex, the potential for liability loss multiplies, and risk management becomes even more critical. Unexpected exposures to loss continuously arise: traces of benzene are found in Perrier, one of the most popular bottled waters imported into this country; someone becomes ill from Tylenol that has been laced with poison; shards of glass are found in a bottle of baby food. These are just a few of the well-known cases in which the risk manager is called in to use all of a company's resources—legal, technical, research and development, public relations—to reduce potential liability losses. The extent to which an organization manages such crises well can be a matter of survival. The Tylenol case, for example, has become a classic case study in good crisis management and good risk management, in this case to protect against loss of public confidence and thus loss of revenue. All industries—food, transportation, banking, manufacturing, entertainment, all manner of services—have risk managers today. In health care, especially, risk managers play a crucial role in crisis damage control.

Risk Management in Health Care

The health care industry has become enormously complex and continues to evolve technologically. Risk managers are often viewed narrowly as the people who review malpractice claims and awards. However, the purview of risk management in today's medical facility is much broader. All potential risks of loss can fall under the umbrella of the risk management office.

If a student is robbed in a medical center housing complex, the risk manager works with security personnel, law enforcement officials, attorneys, and student affairs and public relations departments to respond effectively to the incident and to develop preventive measures for the future.

Risk managers work with insurance brokers or insurance services firms to analyze insurance coverages and ensure that appropriate coverage is in place. In modern health care facilities, the different types of insurance required can number over twenty, of which medical malpractice is only one, albeit an extremely important one.

For emerging technologies, such as infertility treatment, risk managers must keep pace with new theories of liability that may add strange new twists to necessary preventive measures. Similarly, the continuous promulgation of governmental regulations has expanded the regulatory-compliance area of risk management, to prevent avoidable losses from fines and damage to the hospital's reputation.

Finally, when a process involved in delivering health care services is associated with medical malpractice claims and compensatory damages, risk managers must work with everyone involved with that process—physicians, nurses, physician assistants, technicians, administrators, manufacturers of medical products, and so on—to find safer ways to deliver the care. This includes investigating individual incidents to detect specific weaknesses in the system and looking for overall patterns that demonstrate the need for systemic change. Ultimately, risk management involves any activity in an organization that can damage its ability to deliver services safely, its reputation with the public, or its fiscal solvency.

Essential Role for All Clinical, Managerial, and Support Staff. Given the scope of information with which risk managers need to be familiar, it is imperative for them to draw on technical expertise in the health care organization. An effective risk manager sits at the hub of a health care facility's information sources, gathering data that enables him or her to recognize and avoid potentially hazardous situations, evaluating actual and potential claims rapidly to stem financial loss, and calling on expert resources for advice.

The success of a risk management program depends above all on the availability of a network of experts for guidance in developing risk-reducing programs. As a generalist, the risk manager can recognize areas of trouble and make suggestions to reduce hazards, but he or she needs the input of physicians and other clinical and nonclinical personnel to develop procedures that function effectively in the medical arena. Without input from clinicians, management, and support staff who work in the intensive-care units, the emergency rooms, the delivery rooms, the operating rooms, indeed everywhere medicine is practiced, the risk manager is hampered in designing new risk control procedures that are technically feasible, practical, and effective.

Furthermore, the risk manager needs the expertise of clinicians and other front-line personnel to figure out which battles are worth fighting. Zero risk is impossible to attain. Some level of exposure to risk, often a high level, is a reality of the health profession. The most critical job of the risk manager is to determine which potential hazards should have priority, given the limitations of funds, time, and staff available at an institution.

For risks directly associated with invasive procedures or the use of certain technologies, physicians can be key in evaluating where risk management will functionally cut down on financial loss associated with medical care itself; they know where the most injurious errors are common as well as what alternative protocols might reduce injury. Physicians can also be helpful in discouraging the use of risk-management resources in areas where they are least likely to be effective.

No more or less important than physicians are other clinical and nonclinical personnel who can provide information and analysis that bear on how injuries occur in a particular context. Nurses are often in the best position to observe the interaction between medical procedures and the system within which the procedures take place. Technicians who routinely use certain types of equipment may be the first to notice minor defects that can put patients at increased risk. Housekeeping personnel may be more likely to recognize subtle safety hazards on patient care units. Ideally, everyone in the stream of health care delivery is involved in continuous evaluation of the efficacy of services. The current trend in health care toward implementing principles of continuous quality improvement, which require the active involvement of all levels of staff, is congruent with the goals of risk management.

Cooperation between risk management and health care professionals can be extremely fruitful. Ongoing shared data projects have been undertaken by large companies and groups that provide medical malpractice insurance and risk management services. Specialty societies, notably the American Society of Anesthesiology, have also pooled data on malpractice claims to develop a series of safety guidelines to reduce injuries. Such efforts alert all organizations to malpractice claim trends either previously not appreciated or not detectable in individual organizations or small groups of organizations. The UJA-Federation hospitals (located in New York City), through FOJP Service Corporation, have worked together to develop safety guidelines for anesthesiology and are currently working on guidelines for obstetrics.

In the decades to come, such cooperative efforts will be ever more necessary as advances in biotechnology cloud even the most basic assumptions about life and death and make the medical profession more vulnerable to unforeseeable liability losses. Already, previously unimaginable legal battles are being fought over which divorcing spouse "owns" the fertilized eggs stored at their local medical center. Other areas that are or are likely to become grounds for litigation include:

- Decisions on which patients will receive medical treatment available only in limited supply, such as organ donation
- Genetic research and treatment
- Issues related to HIV transmission
- Issues related to death and dying

The future of health care in this country depends not only on governmental regulations and other external forces, but on the ability of health care organizations to direct their finances out of the courts and into the laboratories and hospitals, where the benefits will reach the greatest number of people.

External forces create pressure on the health care system to change, but are not the actual agents of change. In order to stop the current drain of resources to liability claims, risk managers, physicians, other clinicians, and administrators need to work closely together to foresee and avoid preventable losses. The health care risk manager is an ally with common concerns, and ongoing communication is a positive investment toward improving the quality of health care.

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A Century of Progress:

Nursing Quality Improvement at The Mount Sinai Medical Center

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Abstract

Since The Mount Sinai Hospital in New York City began delivering care in the mid 1800s, the medical services and, shortly thereafter, the nursing service have consistently given priority to improving patient care. Through the decades of the late 19th and 20th centuries, the Department of Nursing has remained current with the evolving concept of quality improvement. A historical overview of key elements in the evolution of quality improvement in nursing is presented.

THE MOUNT SINAI HOSPITAL in New York City, a pioneer in medicine since it first began to admit patients in 1852, has been a leader in the provision of nursing care from the day in 1881 when The Mount Sinai Training School for Nurses opened its doors (1). The Mount Sinai Department of Nursing has consistently positioned itself on the evolutionary cutting edge, and reissued in 1991 a statement that affirms: "Nursing's mission is . . . quality nursing care . . . based on documented assessment of needs" (2). This philosophy serves as the foundation for current standards for patient care and nursing practice.

Quality assurance in nursing has shifted from being exclusively centralized in management to empowering the bedside nurse to evaluate and improve care. With the current shift in the health care delivery system from "quality assurance" to "quality assessment and improvement," definitions of quality now include practical measures of performance and conformance to the customer's (the patient's) requirements and expectations. Today, quality care must at the least focus on improving health system processes, require outstanding professional performance by all health care practitioners, demonstrate efficient use of resources, ensure minimal risk to the patient of injury or illness associated with care, and provide for patient satisfaction (3).

A Brief History of Quality Standards and Nursing

The growth and development of standards for quality in hospitals is deeply rooted in the histories of nursing and medicine. An overview of significant factors that have fostered the development of quality in health care provides a context for appreciating its evolutionary nature.

Florence Nightingale, who founded modern nursing, is credited as the pioneer in standard setting. In the 1860s, she analyzed data and demonstrated that the care of British military personnel during the Crimean War was inferior to the care of civilian populations. Through her efforts, changes in sanitation raised standards of health care and reduced mortality for those in the armed forces. Nightingale initiated a process in which standards for nursing were set, actual care was compared to those standards, and action was taken to bring about change. Thus, the process of quality assurance in nursing was born (4).

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Based on the Nightingale model, The Mount Sinai Hospital School of Nursing was one of the first modern U.S. nursing schools (1). The impetus for the establishment of schools for nursing came from the desire to set rules and standards that would upgrade patient care. In hospitals with schools of nursing, care was provided primarily by students, and teaching standards became the standards for the actual provision of care (4). Hospital care thus improved as the result of the close association between hospitals and schools of nursing.

Abraham Flexner's report, published in 1910, revolutionized American medical education, and subsequently patient care. The report acknowledged university medical schools as the leaders of medical research and education, and viewed hospitals' educational role as clinical adjuncts to the universities (5).

Simultaneous with the publication of the Flexner report, organized nursing, structured in state nurses associations, set minimum educational requirements for professional nurses linked to licensing requirements (6). The New York State Nurses Association, founded in 1901, was the first in the nation.

Immediately after World War II, regulatory agencies focused their attention on improving patient care. In 1946, the American College of Surgeons (ACS) set minimum standards for nursing in hospitals which were adopted when the Joint Commission on Accreditation was established in 1951. These became the cornerstone of the Joint Commission's standards from 1953 through 1989.

The Joint Commission later organized their standards into four categories: patient care, leadership, personnel competence and resources, and quality assurance. The first category, addressing patient care, included references to nursing. In the 1940s and 50s, standards stressed safe and efficient care of the patient. In the 1960s, the emphasis shifted to written plans for care. In the 1970s the concept of therapeutically effective care was introduced and in the 1980s, the focus was on organizing the nursing department and establishing standards of nursing practice (7).

The Joint Commission was not alone in setting standards for nursing; professional organizations and the federal government also established requirements for patient care. Nursing leaders urged the profession to regulate itself and control the practice of nursing. The American Nurses Association's Committee on Nursing Service published standards of nursing practice that were used as the model for developing quality assurance programs. Nursing, in the forefront of quality assurance, was considered accountable for and responsible to patients for providing, evaluating, and improving care (8).

The federal government played a key role in monitoring the delivery of patient care. In 1965, when the Social Security Act was amended to create the Medicare and Medicaid Programs, government regulation and standard setting were linked to institutional reimbursement (9). In 1972 an additional amendment to the Social Security Act established professional standard review organizations to evaluate the quality and necessity of health care, determine whether care met professional standards, and determine whether the health care provided was economical and was performed in the appropriate health care setting (ref. 4, p. 16).

Monitoring Quality in Nursing Care

At The Mount Sinai Hospital improving the quality of patient care through interdisciplinary efforts dates back to at least the 1970s. Nursing supervisors were encouraged to meet with their respective medical directors to communicate problems and progress, and to plan patient care programs. On some services, significant progress was made as mutual expectations were clarified and joint objectives were clearly defined. Joint nursing administrative rounds were developed, providing an avenue for coordination to improve the hospital environment and services to patients (10).

Nursing Quality Assurance Program. In the mid-1970s, Mount Sinai's Department of Nursing participated in a federally funded project to systematically and objectively quantify the quality of nursing care. Aided by an outside consulting firm, a scientific instrument with criterion measures based on the central functions of nursing was developed, including valid and reliable measurements of patient care structure and processes based on clinical speciality and patient acuity (11). The use of the tool involves chart review and patient interviews, using random selection, on each patient unit. An assessment is made of patient needs, a specific plan to meet them, and documentation of care given and outcomes expected. Twice a year, a computerized program provides reports detailing the quality of nursing care; results are correlated with each unit's staffing patterns. The new methodology, now in its fifth revision, represented a significant departure from the JCAHO-approved, process-oriented checklist used to retrospectively audit selected patient charts for documentation of nursing care tasks and activities.

Use of this standardized quality monitoring tool marked the beginning of a new age in nursing quality standards. It is among the first such tools ever used in a hospital setting to accurately, systematically, and objectively evaluate the delivery of nursing care. As the era of "benchmarking" begins, the computerized program enables the department to compare the quality of its nursing care with twenty other hospitals across the country. Through the benchmarking process, hospitals can learn from each other how to improve processes related to particular nursing care elements.

In the 1980s, while regulations were being introduced to reimburse hospitals based on diagnosis, the Department of Nursing continued to expand and further refine its newly developed quality assurance program. The decade ended with the Joint Commission initiating significant changes in nursing standards for hospital accreditation. As word of the forthcoming "agenda for change" spread, the department prepared itself for the introduction of unit-based activity on quality.

Unit-Based Quality Improvement. By 1990, a unit-based quality improvement program was implemented throughout the Department of Nursing, utilizing the then-required Joint Commission ten-step model. On each unit, nursing staff prepare a "scope of care" statement that includes descriptions of the size, type, and location of the unit; the major patient diagnoses and procedures, lengths of stay, disabilities, and the major clinical functions and equipment that distinguish the unit. Revisions are made annually, or as patient populations change on the unit. Staff nurses also identify high-frequency, problem-prone, and high-risk elements of nursing care specific to the population served on their unit. They define criteria (indicators) and methodology for data collection and measure progress in improving patient care outcomes. Lastly, they implement interventions (corrective action plans) to obtain improvements.

Generation, distribution, and analysis of unit-specific findings was initiated with the establishment of the program and changes in structure were instituted to empower unit-based nurses to serve as quality assurance representatives and on quality committees. Consultation and collaboration with other clinical departments is an essential element in the development of population-specific criteria, data collection mechanisms, and related action plans. Objective improvement in patient assessment, care planning, patient education, and satisfaction (see below) correlate with implementation of the unit-based structure (12). This program represents a major shift in focus from viewing quality assurance activities as limited to "fault finding" and compliance with bureaucratic requirement, to the broader view of the professional accountability and responsibility of unit staff for improving patient care on the unit.

Patient Satisfaction. Implementation of the unit-based program has resulted in improving patient (consumer) satisfaction with nursing care, as determined by the Mount Sinai Survey Center's quarterly telephone surveys. Quantification of consumer satisfaction with nursing care has been a major institutional concern since at least the 1950s, when survey questionnaires were mailed to patients the day after discharge. In 1966, a computerized version asked such "yes" or "no" questions about the staff nurse as: Did nurses respond promptly when you called? Were they courteous? Were they warm and sensitive to your needs? Was the Nurse in Charge helpful with problems or special requests? (13).

Since 1982, telephone surveys have been conducted quarterly among randomly selected patients up to six weeks after discharge. The new survey tool, revised in 1992, includes the following pretested questions and rates satisfaction with nursing care on a four-point scale (poor, fair, good, excellent): Care and concern of nursing personnel responsible for your care; Attentiveness and response time after asking for assistance; Sensitivity of nursing staff to your health concerns; Willingness of nursing staff to assist you in solving problems related to your care; Nurses' instructions for continuing your care at home; Friendliness of the nurses; Your overall view of the quality of nursing.

Although the current survey methodology represented a major breakthrough in data reliability and validity, results were until recently reported for the entire Department of Nursing—one number for each question and a composite score called "factor nursing"—so that pinpointing individual patient units in need of improvement on specific issues was difficult. Even among nationally conducted surveys by management consulting firms for customer hospitals, nursing-care scores are almost always reported departmentally, not by unit, for each question. In 1990, however, with the initiation of the unit-based quality assurance program, the Mount Sinai Survey Center began to provide unit-specific results. The impact of nursing quality improvement efforts on patient satisfaction is evident in responses to the survey question "Your overall view of the quality of nursing" (Fig.). The rise in scores coincides with the implementation of the unit-based qual-

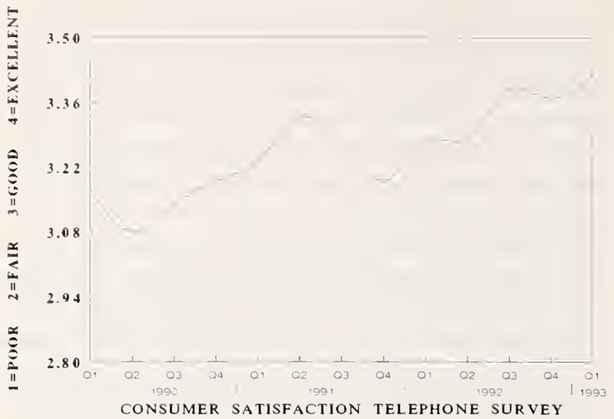

Fig. Overall patient satisfaction with nursing care by quarter, 1990–1993, Mount Sinai Department of Nursing. Rise in satisfaction coincides with implementation in 1990 of a quality improvement program based on data-gathering at population-specific nursing units and the institution of appropriate data-based changes on each unit.

ity improvement program, in which individual units obtain detailed data that is reviewed by nursing staff, who then institute unit and population-specific changes based on the data.

Interdisciplinary Quality Improvement. The Joint Commission continues to require adherence to discipline-specific standards, while emphasizing a greater interrelationship between services to facilitate key patient care functions and outcomes, as evidenced in the 1992/93 revision and consolidation of standards formerly titled "Quality Assurance" into a new chapter titled "Quality Assessment and Improvement," and the addition of two new chapters that are not discipline specific: "Patient Rights" and "Patient and Family Education." Anticipating this new focus, the nursing quality improvement structure is positioned to build on established relationships and to expedite the evolution of collaborative interdisciplinary quality efforts. Nursing, pharmacy, and risk management, for example, are collaborating on developing a medication occurrence data collection system that focuses on improving patient care outcomes.

Nursing's contribution to quality programs has been documented in the annual reports of a number of departments to the hospital's Quality Utilization Assessment and Review Committee. Currently, nursing participates in many multidisciplinary, interdepartmental quality committees (14). In addition, on a number of clinical units, interdisciplinary statements on "important aspects of care" have been developed; and on a variety of services, physicians have incorporated nursing statements on "important aspects of care" into their own quality monitoring efforts. Many of these activities have been facilitated and made possible through the existence of unit-based quality monitoring.

Preparing for the 21st Century

As this century began, the medical and nursing professions were each committed to advancing quality in the delivery of patient care through their separate disciplines. As the century ends a growing body of evidence clearly demonstrates that collaboration facilitates patient care outcomes that cannot be accomplished by nurses or physicians alone through separate quality improvement activities (15–17). Plans are under way for the hospital's Joint Commission review in 1994. At that time, the entire institution will be judged on standards that are based on the concept of continuous quality improvement, which views quality improvement as a journey and not a destination and emphasizes a refusal to settle for meeting minimum requirements and a continuous striving for higher levels of performance. Once again, the professions of medicine and nursing are at a crossroads; this time, however, they must travel the road together as fellow passengers.

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Social Work Accountability:

A Key to High-Quality Patient Care and Services

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"TO BE PROFESSIONAL is to be accountable, to be answerable to someone or to some group, to possess full and complete information upon which to make decisions, decisions that are judgments relating to a program, a population, or a patient and his or her family. In professional terms accountability is the capacity and capability to assume responsibility for those acts and behaviors undertaken to achieve identified objectives. . . . A key characteristic of a profession is that it sets standards for its members' practice. Another is that it monitors professional services, correcting where necessary and, in general, advancing the quality of all" (1).

The social work profession, by origin and mission, has a certain built-in accountability. Jane Addams, Mary Richmond, Bertha Reynolds, their colleagues and successors, established a profession directed toward social accountability nurtured in the apprenticeship nature of social work education, in the refinement of supervisory and consultative processes, in the social controls of practice settings and the standards of the professional association (2). Throughout the first 60 years of this century, the social work profession advanced its accountability through numerous studies of social work practice and the social component of social work in illness and medical care.

At The Mount Sinai Medical Center, the Department of Social Work Services focused applied studies in a number of areas. Department leaders recognized, as early as 1960, the need for information to identify and address service utilization and patient needs in, for example, poliomyelitis and the effectiveness of staff and programs during the epidemic of that disease of the 1950s and 1960s (3); pregnancies in unmarried women, particularly teenage primiparas and multiparas who made great demands on obstetric and social work services (4, 5); and utilization of institutional resources by the elderly, a study that arose out of concerns for quality of care in the face of fragmentation of and poor access to essential services (6). These studies, many of which were funded by grants, were largely descriptive, in the effort to understand who used hospital services and/or the services of individual programs such as social work.

In 1965, the enactment of Titles 18 and 19 of the Social Security Act mandated what previously had been a voluntary process of quality and professional review. By 1972, PL 92-603 established professional review organizations and crystallized requirements for evaluation of the quality of medical care. The field of social work, and the Mount Sinai Department of Social Work Services, anticipated the involvement of and impact on its profession and began, without mandate, evolving toward its own assessment of practice and performance within the structure of emerging requirements for quality assurance programs.

Soon quality assurance requirements became central to the agenda of every federal, state, and national regulatory agency, including the Joint Commission on Accreditation of Healthcare Organizations (JCAHO). Over the past 20 years, the requirements and directives, language and definitions, tools and processes of quality assurance have changed or been modified with startling regularity—in repeated efforts to harness the escalating problems inherent in a health care system beset by spiraling costs, and to improve quality of care and performance within ever-tightening fiscal constraints. In the more than 30 years since it

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first identified the need for studies of the quality of patient care and services, the Mount Sinai Department of Social Work Services has kept pace with these changes, as a leader in its own profession and within the institution.

This article highlights a number of efforts initiated by the Department of Social Work Services that have influenced both the profession of social work and the quality of care and services at The Mount Sinai Medical Center.

New Horizons

When it recognized the imperative to respond to changing health care regulations, the leadership of the Department of Social Work Services at Mount Sinai also realized that the department faced the dual challenge of effectively integrating social health principles into what was essentially a biomedical model of health care delivery and developing a framework for quality assurance that would force social work to create its own quality assurance methodology, including department-specific performance goals, objectives, and measurement criteria. Social work leadership at Mount Sinai believed the challenge could be met by gathering data to support the concept of social health as an integral component of patient care, while simultaneously expanding the existing social work philosophy of accountability during the application of formal assessment mechanisms, including peer review.

Integrating Social Health Principles: Early Studies. A number of social work studies influenced the development of programs and processes at Mount Sinai and at institutions across the country. Among these were studies on patient classification, high-risk screening, and patient satisfaction.

Patient Classification. In 1967, Berkman and Rehr (6) demonstrated, contrary to widely held beliefs within the institution, that elderly hospitalized patients require extensive social service intervention, regardless of income level. Study findings documented a clear rationale for increased social work services to private and semiprivate Medicare patients and resulted in the availability of services to the entire population. This study led to the development in 1972 of a problem-classification system (7) for the hospitalized elderly patient in which 29 problems for adult medical and surgical situations were identified. A validated and updated version of this classification system, applied to all patient populations, has been modified and used by other institutions across the country.

High-Risk Screening. In 1968, Berkman and Rehr developed a screening procedure for early identification of patients and family members facing social and emotional risk related to patient illness (8). Earlier studies had identified a major problem for social workers—dependence on other health professionals to identify patients and families requiring social services; neither sound nor appropriate utilization of services was achieved when social workers relied solely on referral-based systems. One solution was to use screening mechanisms that systematically identified variables associated with "high social risk," which refers to major alteration in the life of the patient or family caused by social or physical stress.

The Department of Social Work Services examined which patients received services, how they reached the department, the types of services received, the types of interventions used, the frequency and duration of interventions, and how workers and patients perceived the outcomes of intervention. In the earlier study of the hospitalized elderly, sociodemographic data revealed that length of stay was significantly related to whether a patient was referred for social services. Although a long length of stay was not in itself a critical factor in referral to the department, it did indicate underlying phenomena related to the need for social services. Social workers in the general and specialized medical, surgical, and pediatric services at Mount Sinai examined extended lengths of stay and analyzed the relationship between severity of illness and impact on the social needs of the patient and family. Through this process they identified a differential scale of social needs of families and patients responding to stress and arrived at general predictions about those who might fall into four identified categories on the scale. This deliberation led to development of the high-risk screening mechanism. Largely as a consequence of this work, early casefinding has been routine at Mount Sinai since 1975.

Preadmission screening for older patients entering the hospital for elective procedures also has been tested as an ongoing program (8A). Publication of the work has had an impact on implementation of similar screening and early intervention programs by social workers in other institutions. The cost-benefit of early casefinding and effective discharge planning cannot be overstated. Social work has contributed to cost containment by reducing length of stay, planning early for patients' posthospital discharge needs, and ensuring that discharge plans are fulfilled by implementing and administering a telephone follow-up program.

Patient Satisfaction. In 1980 (9) and again in 1982 (10), staff in the Department of Social Work Services spearheaded institutional efforts to improve existing mechanisms for evaluating consumer response to care and services. In the original effort, social work researchers sought to improve the disappointing 10% response rate of the existing institutional assessment tool—a questionnaire mailed to patients after discharge with a request that the form be completed and returned in a prepaid envelope. The new questionnaire was designed to produce evaluations that would specify unit locations and services. The researchers also developed a strategy for distributing and collecting questionnaires that would achieve a higher rate of return.

Although changes in the questionnaire and the revised process for distribution and collection produced an encouraging response rate, it became apparent that hospital managers did not find the resulting statistical data useful. Working with these managers, social work researchers revised the instrument to include more specific questions which would provide information to assist in problem solving. In addition, by involving a sample of patients in a pretest of the revised instrument, researchers validated the questionnaire, managers obtained direct feedback from patients, and patients responded positively to direct contact with hospital personnel. The result of the two research projects is an enhanced patient satisfaction survey process.

Developing a Framework for Quality Assessment. Social work leaders at Mount Sinai recognized the need to create a framework for quality assessment that would build on an existing foundation of professional accountability. The goal was to create an atmosphere in which social workers would cleave to and support the concepts of quality assessment and assurance. Success, they believed, was dependent on an interdisciplinary program, although the first step was a functional intradisciplinary program.

They began with the basic tenet that a service department must have objectives that reflect its service delivery in terms of quality, quantity, and cost-effectiveness. Having defined its objectives, the department developed its quality assurance program based on the concept of professional accountability. The basic premise of this concept is that broad-based, in-house studies of service to patients and families and of professional performance are essential to the improvement and maintenance of quality service and programs. To accomplish these studies, the department developed a data-retrieval system on patients and providers, guidelines and standards for chart documentation, a peer review system to assess social work professional performance, and continuing education programs to enhance the knowledge base and improve practice.

Data Retrieval System. Early on, the department gathered information through staff reports on defined activities. Data on direct and supportive services offered to patients and families were stored and reported, first manually and later in an automated data processing (ADP) system.

These mechanisms offered a substantial amount of descriptive information on the range of services and activities undertaken. The ADP system incorporated the use of three forms that had been developed with the participation of practice staff. A registration form captured patient sociodemographic data and worker and service information; a daily transaction form completed by each staff member captured all social work, direct treatment, and supportive modalities for each client; and a change-of-status form covered any change in the case of transfer, closing, or new information regarding the client (11). The data were aggregated and reported monthly to social work staff and administrators, including a listing of cases with activity pattern per case and per case load, location at opening, and services performed by a social worker for a colleague.

Documentation: Foundation for QA Studies. Early in the development of its quality assurance activities, the department recognized that systematic documentation of social services was an essential component not only of patient care but also of successful quality studies. Without consistent data for collection and analysis, it would be difficult, if not impossible, to pursue patient care studies. Prior to 1972, the department had maintained separate social service records, and only brief notes were entered in the medical record. Although this method was useful for periodic communication at critical phases in the course of care, it suffered from lags in communication and lack of continuity (12). The ability to ascertain practice quality also suffered.

Over a period of three to four years in the early to mid 1970s, the department confronted and resolved the issues related to social work documentation in the medical record. These included institutional issues, such as medical staff reluctance to incorporate social service notes and lack of access to and availability of charts; departmental issues, such as resistance to change, insecurity about assessment, fear of recording skills being made public; and concerns about protecting confidentiality of patient information. A departmental committee composed of practitioners, supervisors, and administrators oversaw the process and developed approaches that would help resolve these myriad issues. These approaches included a policy on chart notation that conformed with JCAHO requirements, guidelines for the content of chart notations, a method for implementation, and a mechanism for monitoring entries. The department also initiated a comprehensive education program for social workers, in which skills were developed for clear, concise recording of pertinent psychosocial material.

Peer Review Process. Following the format of the chart notations project, the department explored peer review as a method for evaluating the quality of care and services provided by individual practitioners. In a developmental approach that spanned several months, a peer review committee composed of staff and a social work administrator developed guidelines for a peer review process, a review instrument that would ensure uniform application of the process by assigned review teams, and an implementation plan that included preparation and education of staff. The result of this developmental effort was a retrospective evaluation system that involved random peer review of closed cases to evaluate staff performance from time of initial psychosocial assessment to termination of activity or closing.

Continuing Education Program. In creating its continuing education program, the Department of Social Work Services had as its major goal the development of a "self-directed worker" responsible for his or her own practice and accountable, through quantitative and qualitative measures, for learning and for performance (13). A planning group of staff volunteers interested in the concept of the self-directed program worked with a social work administrator to develop a curriculum for two sets of seminar programs—a general series, using the department's peer review model as a conceptual base for teaching; and a series using the same conceptual framework to teach specific techniques and focus on practice problems (14). The original seminar program focused on entry and assessment skills, collaborative practice, contracting with the client, intervention skills, evaluation of outcomes, and recording skills. In addition, the department created an open-preceptor model that enhanced the traditional supervisory functions and encouraged experienced social workers to develop expertise in a defined area of practice and contract with other social workers to share this knowledge.

The chart documentation project, the data retrieval system, the peer review process, and the continuing education program created a firm foundation that allows the department to modify internal quality assurance processes as external requirements change. Having successfully created a flexible framework for quality assurance during the 1970s, the department enhanced aspects of its various programs throughout the 1980s and developed an effective quality management system for the 1990s.

The Current Quality Management Program

Today, the quality management program of the Mount Sinai Department of Social Work Services is one in which the effectiveness of service delivery is systematically monitored to determine compliance with departmental standards of practice as well as external requirements.

Monitoring of documentation remains an integral component of departmental quality management activities. Although uncertainty exists as to whether quality recording equals quality practice, it is clear first that practitioners who do inadequate assessment and intervention are unlikely to record quality practice, and second that consistent documentation of practice improves the capacity to effectively evaluate practice. The department believes that to focus solely on documentation is to obscure the fundamental objectives of quality activities and therefore recognizes that monitoring of documentation is but one essential component of quality monitoring activities.

As information management systems have become more sophisticated, the original ADP system has been expanded to capture data that enhance the ability of the department to conduct studies of its growing population of clients in the hospital, in ambulatory settings, and in community-based projects. The department derives administrative data about the demographics of its case load and activity patterns from ADP, but uses a wide variety of internal and external information sources to evaluate professional performance and client outcomes.

The peer review process is well integrated into the functions of the department. Although the structure has been revised to accommodate changes in practice, expansion in programs, and increase in staff size, the basic principles remain the same and quality performance the expectation. Supervisory relationships, open preceptorships, and a myriad of continuing education opportunities support quality improvement processes, enhance practice knowledge and skills, and influence programmatic change. While some education programs are mounted as the result of monitoring and evaluation activities, the continuing education structure also allows feedback from staff who identify other topics of interest.

In keeping pace with external requirements, indicators have been developed to monitor care and services, including indicators for such areas as high social risk, alternate levels of care, and impediments to discharge. Indicators are used to evaluate social work assessments and progress notes early in a staff member's involvement with a patient. Timeliness of progress notes is assessed, with particular attention to collaboration, interventions, and patient and family involvement. Each preceptor (supervisor) reviews a select number of charts for each social worker on a quarterly basis. Evaluations are used as a mechanism for continuous monitoring as well as a teaching tool in regularly scheduled supervisory conferences. Problems identified through the monitoring processes are tracked, corrected where possible, and reported to the institutional Quality, Utilization, Assessment Review Committee on a regular basis.

While conforming to requirements for continuous indicator monitoring, the department also conducts broad-based research studies, participates in organizationwide research activities, and is developing practice-based research programs. Among the numerous quality and quality-related studies in progress are decision making in in vitro fertilization, evaluation of adolescent education in use of contraceptives, factors affecting increased length of stay in psychiatric patients, ethnic groups' use of mental health services in school-based programs, the cost of care provided pediatric AIDS patients, evaluation of psychoeducation for psychiatric patients, and an extensive follow-up study of patients discharged from medical and surgical units.

Only by ensuring that the basic elements of quality and accountability were woven into the fabric of day-to-day operations could the department expand its practice purview while continuing to enhance the quality of its care and services. An inherent flexibility ensures its capacity to successfully advance practice and performance improvement in a changing health care environment.

The Future of Accountability and Performance Improvement

Definitions and requirements for quality assurance are "evolving" yet again. The JCAHO, in its 1994 *Accreditation Manual for Hospitals*, published in July 1993, "shifts primary focus from the performance of individuals to the performance of an organization's systems and processes, while continuing to recognize the importance of the individual competence of medical and nonmedical staff members" (15). The *Manual* focuses on a framework for improving organizational functions and creates a new language in which the term "quality" is subsumed by the term "performance improvement." The JCAHO will now focus on "dimensions of performance," which include efficacy, appropriateness, availability, timeliness, effectiveness, continuity, safety, efficiency, and the respect and caring with which services are provided.

Despite changing terminology and processes, the basic tenets of quality management remain the same: continuous monitoring and evaluation based on expected levels of achievement; applying tools to measure performance of functions, processes, and outcomes; and drawing on a comprehensive, integrated information system that collects and analyzes pertinent data. Professionals must have knowledge, skills, values, ethical attitudes and behavior, and resources. They must know costs and management and the meaning of accessibility and availability, as well as understand the principles of quality improvement. They must also have useful data, the knowledge to assess and act on this data, and the opportunity to use informed results.

The Department of Social Work Services believes it is well poised for the future. Its studies have addressed, and continue to address, efficacy, appropriateness, availability, timeliness, effectiveness, continuity, and the respect and caring with which services are provided. Its philosophy of practice is grounded in the tenet that a successful practitioner is a reflective practitioner—one who, within the context of professional standards, continuously examines his or her performance in order to maintain a consistently high level of patient care and services.

In the final analysis, professional accountability is to the client. How this accountability is translated into the definition of "quality" is the key to successful performance improvement programs. When the individual professions, like social work, hold themselves accountable for their performance, the institution's ability to measure the overall performance of the organization is greatly enhanced.

Acknowledgments

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Patient Representation as a Quality Improvement Tool

Ruth Ravich, B.A., and Lucy Schmolka, M.A.

Abstract

In the late 1960s, healthcare institutions began to appoint patient representatives, also called patient advocates or ombudsmen, to counter complaints about unsatisfactory and impersonal delivery of care. Patient representatives are now employed in over half the hospitals in the United States as well as in nursing homes, clinics, health maintenance organizations, and other health provider organizations. At The Mount Sinai Hospital in New York City, the Patient Representative Department was established in 1966 to provide greater access to the institution for community residents, to help solve patients' problems and complaints, and to serve as a quality assessment and improvement tool. It functions as both a proactive and reactive force, addressing patients' concerns, investigating sources of dissatisfaction, recommending corrective action when policies and procedures are not responsive to patient needs, and striving to create a patient-friendly environment.

Academic medical centers offer an impressive array of technology and services devoted to achieving state-of-the-art, skillfully delivered healthcare. Patients and their families, however, may be intimidated by the size and multiplicity of resources, which create an impersonal, fragmented, and mechanical environment. Individual attention is difficult to provide as staff members, pressed by the demands of financial constraints, regulations, and paperwork, have become more function-oriented than patient-oriented. Patient representation is one way that healthcare institutions have countered the feelings of fear and resentment with which patients react to the depersonalization of the hospital experience. Patient representatives have become an integral component of patient care, working both to allay the anxiety engendered by illness and hospitalization and to recommend changes in the delivery of services.

The Emergence of Patient Representation

The concept of patient advocacy began to take shape during the 1960s as an outgrowth of the civil rights and consumer movements. At that time it was believed that ethnic minorities and the "poor" required special help in accessing and negotiating the healthcare system. Today it is recognized that the system is difficult for all, and many patients, regardless of educational or economic status, need assistance.

The Patient Representative Department at The Mount Sinai Hospital in New York City, created in 1966, pioneered the concept of patient advocacy in healthcare institutions. Based on the ombudsman model and on information and referral services (1, 2), it was established to bring people and services into closer contact and thereby reduce alienation of the public and insulation of the hospital staff (3). The Mount Sinai department was a major force in the organization of the Society of Patient Representation and Consumer Affairs of the American Hospital Association. Its procedures and methods of data collection have provided the basis for programs throughout the United States and abroad, as well as the country's first Masters Program in Health Advocacy, estab-

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lished at Sarah Lawrence College, Bronxville, NY, in 1980.

Patient representatives now function in over half the nation's hospitals as well as in clinics, nursing homes, health maintenance organizations, and other health provider organizations. They focus not only on patient satisfaction but also on quality assurance and improvement. As both a proactive and reactive force, they serve to create a patient-friendly environment; to avert problems in advance; to solve them, should they occur; to propose system revision to reduce the possibility of recurrence; and to recommend changes that will improve the institution's responsiveness to its consumers.

Although current literature discusses patient-centered care as an important new trend, such care has been a goal of patient representation since its inception. Patient satisfaction surveys, the traditional means of gauging how well a hospital is responding to patient needs, are now augmented by surveys that allow patients to go beyond rating their care (soft data) to reporting about their care (harder data that can be tied to specific events and actions) (4). Patient needs "as patients perceive them—not as professionals or hospitals do" provide critical input for assessing performance (5). Because patient representatives are directly involved in issues of patient care and of services, they are in a position to document and provide this information to hospital management. Although they have no direct authority to implement change, the prominence of the position in the institution can be used to solve problems for patients and make recommendations for change (6).

Patient Representation and Quality Assurance

The Patient Representative Department at The Mount Sinai Hospital operates across medical, paramedical, and nonmedical lines and deals with all levels of personnel and services. It provides a centralized and visible mechanism for airing and addressing patient and family grievances, as required by the New York State Health Code and by the JCAHO. Because of its unique role and wide perspective, the department can assess the institutional climate and help to promote cooperative response to patient needs (7). Although institutionally sponsored, the department is positioned to act as a gadfly to the directors and managers of medical, ancillary, and administrative services, providing these managers with a consistent focus on patients' perceptions of care and on recurrent patient problems, complaints, and unmet needs.

Patient representatives are essentially problem solvers—for individuals, departments, and systems. The issues they address range from diet to dying, from conflict arising from interpersonal communication to major organizational flaws. They interpret policies and procedures to patients, families, and visitors and help guide them through the elaborate maze of the hospital world. They act as liaison among patients, families, and staff in cases of dissatisfaction with services and potentially litigious situations. They support staff by intervening in response to difficult and complicated patient-family problems and concerns and provide linkages that bridge the inevitable gaps within the system.

Results are achieved through the patient representative's ability to listen objectively, knowledge of the formal and informal rule systems of the institution, and the capacity to generate cooperation across departmental lines and minimize institutional red tape. The roles of the patient representative as ally and advocate for the patient are performed in a collegial context, using persuasion and negotiation rather than confrontation and demand (6). By considering the needs of the patient and family, as well as the concerns of the staff and the capacities of the institution, a workable solution can usually be found, even in complex situations.

A critical element of the patient representative's job is to facilitate communication between patient and staff. When a problem is presented, the patient representative aims at finding a solution as expeditiously as possible, investigating the source of concern while keeping the patient and family out of the center of the conflict. Resolutions range from a room change or clarification of dietary orders to calling a physician who, according to an irate patient or family, has not visited for several days. If a patient's health care team—doctors, nurses, social workers—is making decisions with which the patient or family disagrees, that disagreement may stem from a misunderstanding of the team's rationale or because no one has elicited the patient's perception of his or her needs.

At Mount Sinai, patient representatives are available to all who use medical center services. Referrals are initiated by patients and their families, hospital staff, and community agencies. For inpatients, an orientation booklet describes the program and how it can be accessed. A patient's hotline, clearly identified on the bedside telephone, connects them directly to the department.

Walk-in offices are strategically located at clinic and emergency room sites for patients using ambulatory services.

Continuous Quality Assessment. As a means of continuous quality assessment, patients' complaints and unmet needs are sorted into 20 primary categories and subdivided to provide greater detail. A computer program identifies monthly trends in patient problems and complaints by department and nursing unit. Given the approximately 16,000 cases with which the department deals annually, it can provide specific documentation on persistent problems, gaps in services, and areas of unresponsiveness to patients and families.

When statistics point to systemic problems, customized reports can be supplied to the departments involved. These include the number and types of problems and the areas or nursing units in which they have occurred. By investigation and analysis of lapses in or implementation of systems, patient representatives can formulate recommendations for change. These can be discussed with department managers, who are in a position to make appropriate revisions in policies and procedures or to institute staff training. Patient representatives often assist in applying and monitoring these revisions. They also participate in in-service education on patients' and families' perceptions of "the experience of illness, the incapacity to do what one would ordinarily do" (8).

In addition to approaching systemic problems with individual managers, a report of trends in patient perceptions of care is prepared for review by hospital administration and the Quality Assurance Committee of the Board of Trustees. The most frequently referred and the most time-consuming categories of complaints, problems, and concerns with which the department deals are:

- Communication and personal interaction with physicians and nurses
- Timing of treatment and care
- Patients' rights and advance directives
- Dissatisfaction with room, roommate, or frequent room change
- Admissions and discharges
- Ancillary services (radiology, laboratories, medical records)
- Diet, housekeeping, and climate control
- Billing disputes
- Equipment availability (wheelchairs, stretchers)

Continuous Quality Improvement. Besides providing data to assess quality, patient representatives are in a position to directly affect it. Patient-family encounters, the environment in which services are delivered, the sensitivity and concern of staff, and the stresses of illness can influence the consumer's perception of his or her overall experience. Every direct and indirect interaction with a member of the staff forms a crucial link in the patient's impression (5). The patient representative—whose help is sought when there is a breakdown in the patient-family-provider relationship—has the opportunity to significantly improve the patient's satisfaction with services. If he or she does the job well, the consumer's impression of the hospital as caring and responsive is enhanced.

In addition to problem and complaint resolution, the department provides many other services each year that assist patients and staff and help to improve the institution's relationship with its patients and its community. These services, some provided to comply with federal and state law, include informing patients about their rights and the opportunity to establish advance directives (the New York State Health Care Proxy); informing patients about resources in the hospital and the community; providing notary, check cashing, and interpreter services; and offering support to patients and families. Patient representatives are also frequently called on to support staff members when they encounter "difficult" or possibly "litigious" patients and families who may be disruptive to the functioning of the patient unit, ambulatory service, or ancillary area.

To help create a pro-consumer environment at Mount Sinai, the department also participates in orientations for new employees and in-service staff training. Subjects covered include patients' rights, the New York State Health Care Proxy, and special services offered at Mount Sinai for patients with speech and hearing disabilities and those who are non-English-speaking. Sessions often focus on patient and family perceptions of the hospital experience and the need for staff sensitivity to patients' and families' concerns and values, whether or not these concerns and values are in accord with caregivers' attitudes.

Some of Mount Sinai's services taken for granted today are the result of the Patient Representative Department's input into the revision of institutional programs to better address patient and family needs. Many changes, some now mandated by state and federal legislation and third-party payers, were originally initiated because of patient representative awareness of patient needs. In the provision of medical services, the department was instrumental in shifting medically indicated circumcisions and certain breast biopsies from the inpatient to the outpatient setting to eliminate long waiting periods for admission to the hospital. The department also promoted patients' acceptance of care by residents and senior medical students by including an explanation of their role in teaching hospitals in the "Welcome to The Mount Sinai Hospital" booklet. In the psychosocial area, changes included distribution of the "Patient's Bill of Rights," encouragement of patients to become active partners in their health care, and the creation of a staffed waiting area for families of surgical patients. On a systems level, the hospital discharge form was revised to include a copy for the patient—a modification that not only serves to educate patients and improve follow-up care in the emergency room and clinics, but also to consolidate information and reduce staff time and costs entailed in the multiple forms previously used (9).

More recently, at the department's suggestion, focus groups were organized to include patients in critiquing hospital care. Also, in response to patient and physician requests for better channels of communication, the Patient Representative and Human Resources departments arranged a series of programs for faculty practice and private physicians' office staffs designed to provide updated information about hospital systems and procedures, so that staff members could present their patients with a realistic picture of what should be expected from the hospital experience.

Other changes introduced through patient representative intervention include:

Improvement of services and comfort for surgical patients held in the Recovery Room for long periods (sometimes overnight) after they are medically cleared for discharge to a unit because beds are unavailable. Families are now allowed limited visitation, and information and support have been enhanced.

Clarification of guidelines for nursing staff on removal of patients' contact lenses prior to surgical or other procedures by the Director of the Department of Ophthalmology.

Expediting patient requests for release of medical information by making authorization forms available on nursing units (in addition to the Medical Records Department).

Restriction of access to patient census lists at hospital entrances to hospital personnel; these lists had been available to visitors, jeopardizing patient confidentiality.

Allocation of clinic appointment slots to Emergency Room personnel for scheduling patients referred to a clinic for follow-up. Confirmation of the appointment is now provided to the clinic, so that medical charts and x-rays can be requested in advance.

Establishing a procedure for clinic clerks scheduling appointments to ask patients whether x-rays had been or would be taken prior to their next visit. Radiology Department staff time was thus saved by eliminating attempts to retrieve nonexistent films.

Rewording of notice on food trays informing patients of food substitution from a statement that the substitution "conforms with the physician's diet instructions," leading patients to conclude that their diet had been altered by the physician due to a change in their medical condition, to a statement that the substitution is "due to circumstances beyond Dietary Department control."

Maintaining continuity of care for patients who cannot pay in advance, as required by hospital policy, and reducing possible hospital liability by making special financial arrangements for patients requiring clinic follow-up after emergency room care or hospitalization.

Conclusion

Operating within the dual perspectives of institution and consumer, patient representatives are important components in continuous quality assessment and improvement. They provide direct information and support for individual patients and their families and help the institution respond effectively to issues and concerns. They track, trend, and analyze recurrent system problems and, by working with administrative personnel, effect appropriate changes. They provide linkages among the various components of the hospital and between the institution and the communities it serves. They identify unmet needs and suggest innovative programs to attract and accommodate diverse patient populations. They facilitate education, communication, and cooperation toward the overall institutional goal of promoting a positive consumer-provider relationship.

Finally, the presence of the Patient Representative Department makes a definitive statement to patients, their families, community agencies, and medical center staff that management is patient-oriented, concerned, willing to listen and, when appropriate, take action to resolve problems, conflicts, and misunderstandings. It indicates that management is committed to improving the hospital experience both in reality and in perception. A successful patient representative program plays a critical role in increasing the organization's overall responsiveness to patient interests and in reducing the sense of alienation often perceived in the modern medical center environment.

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Prevention of Medication Errors

Developing a Continuous-Quality-Improvement Approach

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Abstract

Medication errors can be a serious problem that exposes patients to preventable risks. Although medication errors are often considered primarily a nursing issue, every health care provider plays an important role in medication error prevention. A continuous quality improvement philosophy with involvement of a multidisciplinary team is the optimal method for identifying and correcting the causes of medication errors. Careful analysis of the medication distribution system and identification of system flaws is an integral part of the continuous quality improvement process.

MEDICATION ERRORS are unwelcome and undesirable adverse clinical events that are a common cause of poor-quality patient care in health care facilities (1–4). Medication errors expose patients to additional but preventable risks, frequently leading to an increase in hospital stay, and in some cases contribute to morbidity and mortality (5, 6). These errors compromise the patient's and public's confidence in the health care system and are one of the leading causes of drug-related iatrogenic illnesses (2, 4, 7). Errors in drug administration and treatment account for up to 30% of liability claims against insured hospitals, with an average award of $18,273 per medication-error related claim (8, 9). Because of its impact on quality of care and the economic welfare of the health care system, reduction of medication errors is an important goal for all health care facilities. This article provides an overview of the problem, including prevalence, system for categorization, roles of the various health care providers in prevention, and the development of a continuous quality improvement program to address this issue in a large teaching hospital.

Definitions and Systems

According to the American Society of Hospital Pharmacists, medication errors can be broadly defined as doses administered to a patient that deviate from the prescriber's medication order (7, 9, 10). With the exception of errors of omission (discussed below), the dose must be received by the patient to be categorized as a medication error; therefore, medication errors that are prevented or avoided are not generally included in reported error rates. Errors in prescribing are generally evaluated separately from other medication errors, but they are an integral part of the problem (9).

The frequency of medication errors is difficult to estimate from reported studies because of variations in methodologies and definitions of error categories (9). In addition, errors that do not result in adverse patient outcomes are also included in the numbers reported, and may in fact represent the majority of reported errors. Error rates from 1.7% to 59% have been reported in observational studies (including wrong-time errors), depending on the system of drug distribution in use. Results from studies in the United States, the United Kingdom, and Canada have generally indicated an error rate as high as one medication error per patient per day (excluding wrong-time errors) (9). The studies by Barker et al. and Hynniman provide the generally accepted rates of error: 15% for floor stock distribution sys-

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tems and 2%–5% for unit-of-use distribution systems (11, 12).

There are several known causes of medication errors (7), including:

- illegible handwriting; use of abbreviations
- look-alike or sound-alike names and packaging
- ambiguity in strength or directions for use
- transcription, calculation, and labeling errors
- staff inadequately trained or has excessive workload
- medication unavailable
- equipment or system failure

Examples of drugs with similar names that can lead to errors:

- Tolazamide—Tolmetin
- Platinol—Paraplatin
- Chlorpromazine—Chlorpropamide
- Etidronate—Etomidate
- Vinblastine—Vincristine
- Acetohexamide—Acetazolamide
- Diamox—Diabinese
- Paxil—Paclitaxel
- Solumedrol—Solucortef
- Norflex—Norflox (Norfloxacin abbreviation)

Most medication errors are largely reported as errors in drug administration, often implicating the nurse as the responsible party (13). Drug administration, however, is only part of a system of medication-related events that begins with prescribing the drug, and in fact the sources of medication errors are multidisciplinary and multifactorial.

Nine categories of medication errors have been defined by the American Society of Hospital Pharmacists (7, 9).

Prescribing. Errors in dose, dosage form, quantity, route, concentration, rate of administration, directions for use, drug selection based on indications, contraindications, known allergies, and existing drug therapy ordered by the prescriber.

Omission. The patient fails to receive medication by the time of the next scheduled dose. A patient's refusal to take the medication is not considered an error of omission.

Wrong Time. The patient does not receive his or her medication within a predefined time interval, for example within 1 hour of the scheduled time. This interval is based on the average time required for a nurse to prepare and administer doses for a unit during a typical medication pass. It is established by each individual health care facility, taking into consideration what they consider acceptable. Although the significance of wrong-time errors has been questioned and some authors do not include this data in studies of medication errors, these errors can be therapeutically important for drugs which require serum drug level monitoring or maintenance of a certain minimum effective serum drug level.

Unauthorized (Unordered) Drug. A patient receives a drug not authorized by the patient's prescriber. Examples include wrong drug, a dose given to the wrong patient, and unordered drugs.

Improper Dose. A patient receives a dose greater or less than the amount prescribed, or duplicate doses are administered to the patient. Allowable deviations (ranges) of doses measured by delivery devices should be set by individual health care facilities to account for variations inherent in the design of these devices. Exclusions include topical applications when amounts are not expressed quantitatively.

Wrong Dosage-Form. Administration of a drug to the patient in a form different from that prescribed—for example, administration of an intramuscular depot dosage form intravenously.

Wrong Drug Preparation. Errors in preparation or manipulation of a drug prior to administration, including errors of reconstitution and dilution (including failure to shake a suspension), combining drugs that are physically or chemically incompatible, and inadequate packaging, such as failure to protect drug from light.

Wrong Administration Technique. Drugs administered via the wrong route, via the right route but wrong site, such as in right rather than left ear, via the right route but incorrectly administered, for example an intravenous bolus instead of infusion or a failure to intravenously push a drug over designated time, or the use of poor technique, including failure to wipe the skin with alcohol prior to an injection, or using improper inhalation technique.

Deteriorated Drug. The physical or chemical integrity of a medication has been compromised, including expired drugs and medications that require refrigeration but were left out at room temperature.

In 1986, the Joint Commission on Accreditation of Healthcare Organizations (JCAHO) adopted the "Agenda for Change," a commitment to improve the quality of patient care by monitoring, evaluating, and improving the actual performance of health care organizations, giving less emphasis to the individual's capacity to perform (14–16). Actual performance is measured using performance indicators which focus on appropriateness, effectiveness, and interdepartmental and

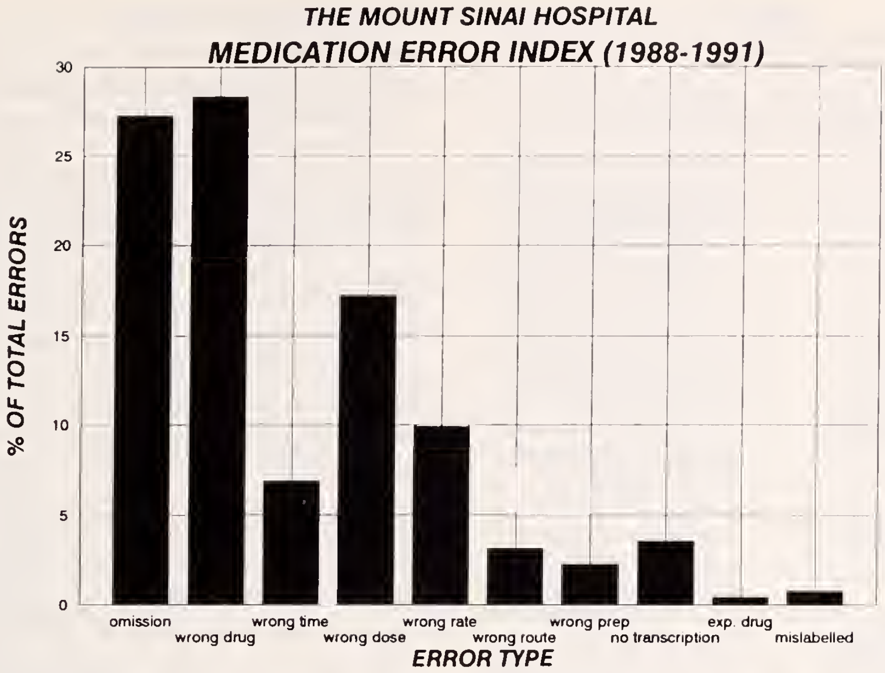


Fig. 1.

other aspects of quality of care (14). Eight areas directly related to patient care have been identified by the JCAHO Taskforce for development and testing of these indicators (14). One of these eight areas is medication use, which includes drug distribution (14–16). The goal of medication distribution systems is to ensure the safe, effective, and efficient use of drugs (14). A reduction in medication errors and an improvement in medication dispensing and administration will play an important role in achieving this goal. An effective drug distribution system and multidisciplinary efforts on the part of physicians, nurses, and pharmacists are also required to attain this goal.

The Roles of Health Care Providers in Preventing Errors

Physicians. As medication prescribers, physicians can play a key role in preventing medication errors by incorporating some basic precautions into their prescribing habits (4, 7). All medication orders should be clear and complete, including patient's name, drug name, route and site of administration, dosage form (where applicable), schedule, and name of prescriber. It is important to review drug orders for accuracy and legibility immediately after prescribing. Ambiguous orders, such as "take as directed" or "take five tablets," should be avoided and replaced with specific directions and dosage strengths (e.g. "mg", as required).

The use of abbreviations, including unapproved abbreviations of drug names and chemical names, should also be avoided, and decimal expressions should be carefully recorded:

- "qd" (daily) has often been misinterpreted as "qid" (four times a day), "qod" (every other day), or "od" (right eye)
- "AZT," an unofficial name, has been interpreted as aztreonam, zidovudine, or azathioprine
- "6-MP" has been misinterpreted as six tablets of mercaptopurine
- "U" for units has been misinterpreted as a zero following the desired dose and should not be used in medication orders; it has led to administering ten times the dose of drugs like insulin—6 U can be interpreted as 60 units
- A leading "0" should precede the decimal expression of less than 1 (e.g., 0.5 mL, 0.50 mcg)
- A terminal "0" should never be used (e.g. 5.0 mL).

Verbal medication orders should be reserved for emergency use when written or faxed orders are impossible. Numbers (for dose, frequency, or duration of therapy) in the teens are commonly misheard as multiples of ten (15 mEq misheard as 50 mEq). It may be helpful to spell out these numbers to the receiver when communicating the order. In addition, verbal orders should always be read back to the prescriber by the receiver.

Furthermore, physicians should be familiar with a hospital's medication ordering system and

TABLE
System Problems Identified by the Taskforce

Problem	Suggested resolution
Lack of uniform procedures in medication administration from one unit to another	Assess current unit differences in medication administration procedures by developing a survey instrument. Determine methods to standardize procedures to minimize errors
Limited pharmacy involvement in the medication incident reporting and tracking process	Weekly summary of errors to be prepared in the Department of Pharmacy, to be used to determine system defects that may be correctable
Controlled drugs frequently involved in unordered drug errors	Investigate automated dispensing systems to minimize errors with controlled substances
Use of unofficial abbreviations for drug names identified as a source of several unordered drug errors	Form a subcommittee of the Pharmacy and Therapeutics Committee to review this issue and recommend appropriate action
Use of Latin abbreviations such as QD, QOD, and OD and abbreviation U for units identified as a source of errors	Subcommittee of the Pharmacy and Therapeutics Committee to prepare recommendation on use of abbreviations
Physician order sheets were not removed from patients' charts, therefore pharmacy Kardex was not complete and accurate	Data to be collected to identify areas where this is most common; corrective measures to focus on these areas

policies, standard administration times, and institutional drug and treatment guidelines if they exist.

Pharmacists. Pharmacists can prevent medication errors by reviewing medication orders for therapeutic and medication administration appropriateness, safety, and rationale (3, 7, 17–19). Pharmacists should avoid assumptions regarding ambiguous and confusing orders and should contact the prescriber as required. A self-check of the medication order, the drug product, labeling, and dosage calculations prior to dispensing the medication is a wise practice. Pharmacists should also routinely review unused returned medications to help identify system breakdowns, such as errors of omission.

In addition to these recommendations, pharmacists can improve patient care by monitoring drug therapy and reviewing patient medication profiles and clinical status for possible drug interactions, adverse events, dosage adjustment, contraindication, and allergies. Pharmacists should have an active function in drug use evaluation and also in developing treatment guidelines for medications, where applicable.

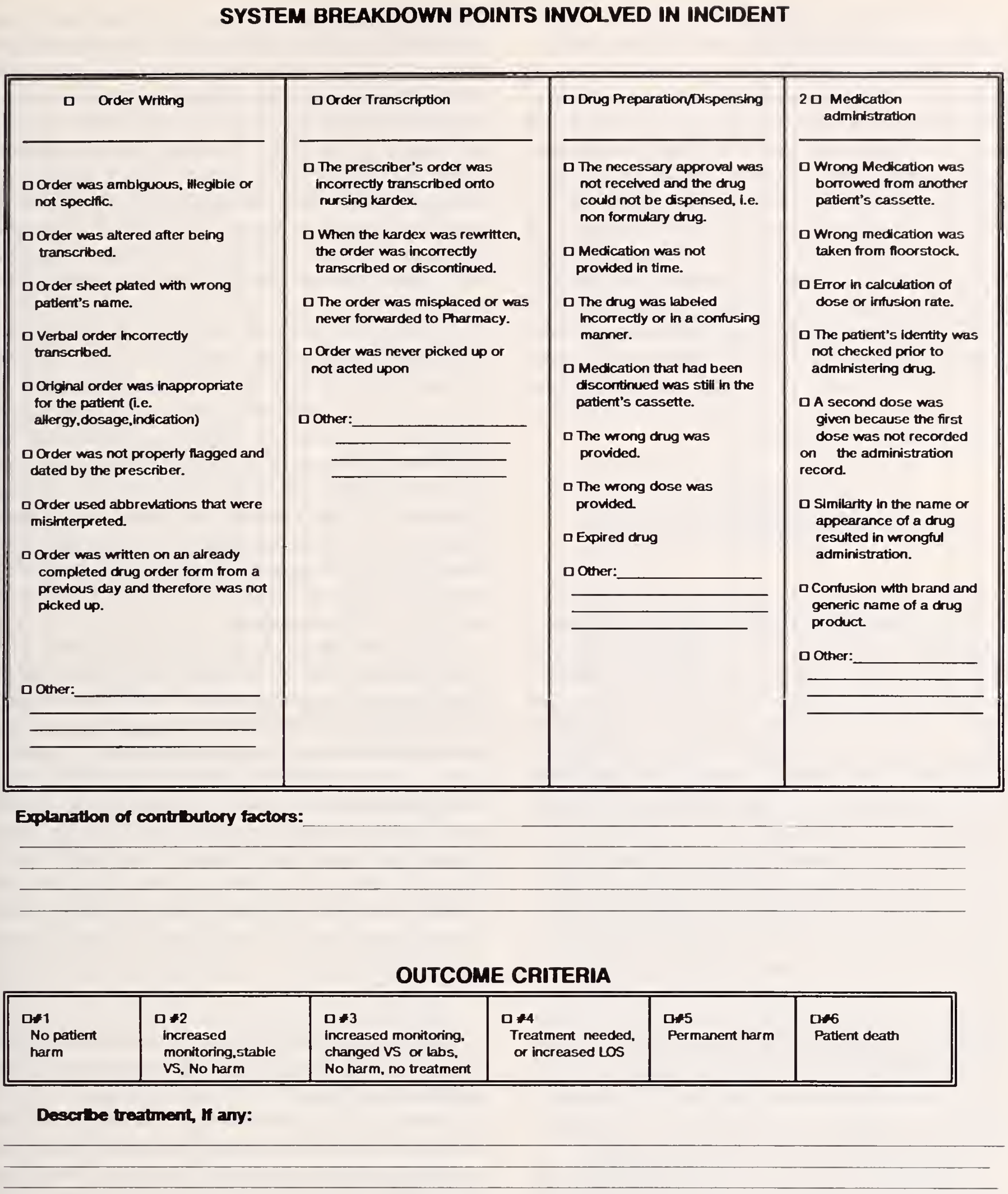
Nurses. Nurses are strategically located to detect and reduce medication errors because they are directly involved in patient-related and medication-administration activities (6, 7). As such, they serve as the final check-and-balance point for medication errors. Nurses should be familiar with the medication use process at their institution. The drugs dispensed should be checked against the drug orders prior to administering the medication for patient's name, drug, dose, dosage form, administration route and site, and schedule. Medication calculations should be self-checked, and complicated calculations (those that require more than one calculation) should be double checked by another nurse or pharmacist. Ambiguous and confusing orders and unfamiliar dosages or routes should be questioned so that all medications can be administered with confidence.

Prior to administration, nurses should also inspect the integrity of the drug by examining expiration dates, general appearance, and particulate matter in intravenous solutions. Medication doses should not be removed from packaging or labeling until immediately before administration, and there should be no borrowing of medications from one patient to another.

The Role of Drug Distribution Systems in Error Prevention

There are several types of drug distribution systems, the oldest being the traditional one (complete floor stock distribution or individual prescription order) and the unit dose system (11). In the floor stock distribution system, medication orders are rarely reviewed by a pharmacist prior to medication administration. In general, drugs are dispensed in bulk quantities to the nursing unit, allowing potentially lethal doses of drugs to be present on the units with no restrictions. This is problematic, especially when approximately 80% of nurses were reported to be unable to perform medication calculations at a 90% proficiency level (20).

In the unit dose distribution system, individual patient-specific doses of drugs are prepared, packaged, and labeled in ready-to-administer forms and are stored in individual patient-specific medication cassettes (11). Each medication order is reviewed by a pharmacist, and a limited supply of drugs (usually a 24-hour supply) is dispensed to the nursing unit (21, 22).



SYSTEM BREAKDOWN POINTS INVOLVED IN INCIDENT

☐ Order Writing

- ☐ Order was ambiguous, illegible or not specific.
- ☐ Order was altered after being transcribed.
- ☐ Order sheet plated with wrong patient's name.
- ☐ Verbal order incorrectly transcribed.
- ☐ Original order was inappropriate for the patient (i.e. allergy,dosage,indication)
- ☐ Order was not properly flagged and dated by the prescriber.
- ☐ Order used abbreviations that were misinterpreted.
- ☐ Order was written on an already completed drug order form from a previous day and therefore was not picked up.
- ☐ Other:____________________

☐ Order Transcription

- ☐ The prescriber's order was incorrectly transcribed onto nursing kardex.
- ☐ When the kardex was rewritten, the order was incorrectly transcribed or discontinued.
- ☐ The order was misplaced or was never forwarded to Pharmacy.
- ☐ Order was never picked up or not acted upon
- ☐ Other:____________________

☐ Drug Preparation/Dispensing

- ☐ The necessary approval was not received and the drug could not be dispensed, i.e. non formulary drug.
- ☐ Medication was not provided in time.
- ☐ The drug was labeled incorrectly or in a confusing manner.
- ☐ Medication that had been discontinued was still in the patient's cassette.
- ☐ The wrong drug was provided.
- ☐ The wrong dose was provided.
- ☐ Expired drug
- ☐ Other:____________________

2 ☐ Medication administration

- ☐ Wrong Medication was borrowed from another patient's cassette.
- ☐ Wrong medication was taken from floorstock.
- ☐ Error in calculation of dose or infusion rate.
- ☐ The patient's identity was not checked prior to administering drug.
- ☐ A second dose was given because the first dose was not recorded on the administration record.
- ☐ Similarity in the name or appearance of a drug resulted in wrongful administration.
- ☐ Confusion with brand and generic name of a drug product.
- ☐ Other:____________________

Explanation of contributory factors:____________________

OUTCOME CRITERIA

☐#1 No patient harm	☐ #2 increased monitoring,stable VS, No harm	☐ #3 increased monitoring, changed VS or labs, No harm, no treatment	☐ #4 Treatment needed, or increased LOS	☐#5 Permanent harm	☐#6 Patient death

Describe treatment, if any:____________________

Fig. 2.

Medication error rates in traditional distribution systems and unit dose distribution systems have been compared by Hynniman et al. (11) and Barker et al. (12). Direct observations, by an objective reviewer, of nurses preparing and administering medications to patients were used to detect and report medication errors. The medication error frequency ranged between 10% and 20% in traditional systems, compared to 2% to 5% in unit dose distribution systems ($p < 0.05$). Errors of omission and dose were the most common medication errors (9, 12, 23, 24). In some hospitals, the unit dose system has reduced error rates to as low as two to three errors for each patient per week (5).

Although implementing these recommendations will reduce medication errors, a system is needed to capture medication errors which do occur and to identify sources of medication errors or system breakdowns so they may be rectified (7, 14). This mechanism is consistent with the intent of JCAHO's "Agenda for Change"—to improve the quality of patient care on a continual ongoing basis. In most health care facilities, medication errors are reported voluntarily to quality assurance and utilization committees (25). Unfortunately, the number of medication errors reported probably do not reflect the actual number of medication errors that have occurred (7, 9, 15, 26). Barker and colleagues evaluated the detection of medication errors using direct observational technique. They found that 29% of medication errors committed were never reported because the nurse was unaware of the occurrence of an error or feared punitive consequence (26).

Developing a Continuous-Quality-Improvement Approach

Some of the reluctance to report medication errors may stem from incident reporting systems in hospitals which focus on assigning blame to individuals rather than on strategies for identifying and correcting deficiencies of the system (26). Concentrating corrective measures on the individual involved may improve that individual's performance, but will not necessarily affect the future performance of the system or of other health care providers who use it (12, 22). The foundation of medication incident reporting systems in hospitals should instead be a continuous quality improvement process. Continuous quality improvement (CQI) is a multidisciplinary and systematic approach to summarizing, analyzing, and evaluating data which enables change to be made as necessary. CQI does not focus on blame, but rather concentrates on the causes of a problem and develops strategies to prevent recurrence. The assumption is that the performance of individuals using the system will be influenced by the quality that is built into the system.

Development of a CQI Approach at The Mount Sinai Hospital. In the past, the medication incident reporting system at The Mount Sinai Hospital in New York City has largely involved categorizing incidents by type, such as wrong drug administered, wrong dose administered, omissions, and so on. Corrective measures mostly focused on the individuals or units involved. Data on possible system deficiencies contributing to the incident were not collected in a form allowing easy identification of needed system improvements. Since nurses at the institution are usually responsible for the final step in the medication distribution process, and most problems are identified at this point, the majority of medication incident reports were initiated by nurses. The system for tracking and addressing problems was therefore handled almost exclusively by the Department of Nursing. The Department of Pharmacy became involved when an error in dispensing occurred or when a serious error resulted in significant patient harm. Prescribers were not usually involved, other than being informed when an error involved a patient under their care.

Although the number of reported medication incidents at Mount Sinai had been small in relation to the total number of doses administered (approximately 450 medication incidents annually, the total number of doses administered being 5 to 6 million), it became apparent that the reporting system did not include all errors that occurred or the reasons for their occurrence. Therefore, an interdisciplinary Medication Incident Taskforce was created by the hospital to review the existing system and determine the direction for future actions.

The taskforce was made up of representatives from nursing, pharmacy, risk management, quality assurance, and the medical staff. The first step for the taskforce was to review data from previous years and what was known in regard to types of errors, occurrence rates, drugs involved, causes of errors, etc. In all, approximately 1,000 medication incidents were reported during the three years prior to the study period, the most common incident being administration of an unordered drug. Controlled substances were highly represented in this group. A bar chart of this data was prepared based on a review of reports from this period (**Fig. 1**).

It became clear to the taskforce that information regarding the root cause or system deficiencies that may have led to particular errors was less than complete. The taskforce agreed that a continuous quality improvement model would be the most appropriate for addressing any deficiencies that existed in the medication control process. The philosophy inherent in this approach as it applies to medication incident tracking and analysis is, briefly:

- What went wrong, not who did wrong
- Customer oriented
- Systems approach to problem
- Change everyone's behavior, not just one individual's
- Ask repeatedly why event occurred—find root cause of problem, not just what happened

The taskforce agreed that the ability of health care providers to perform within the medication distribution system was affected by the structure and quality of the process. The larger system in which medication administration functions are performed would need to be carefully evaluated in order to improve the end result.

Early in 1992, a system for more timely review and analysis of medication incidents was initiated. The departments of pharmacy and nursing closely collaborated in identifying problems that could be addressed through modification of the current medication administration system. Based on information collected during this period, several problem areas were identified. Some of these problems and their possible resolutions are listed in the **Table.**

It also became apparent that new mechanisms for collecting information and identifying the root causes of medication incidents were needed. The form that had previously been utilized for reporting incidents needed to be modified to facilitate the process of identifying and tracking common system breakdown points and other pertinent information. Revision of the information on the report form would also ease the entry of the data into a database for the tracking process. In addition to complete demographic data, information on possible causes of error and standardized definitions of outcome were added to the data collection instrument. This was accomplished by dividing the medication administration process into separate functions. The functions identified were order writing, order transcription, dispensing by the pharmacy, and administration to the patient. Within these areas, several possible breakdown points were identified, based on suggestions of the taskforce and previously reported incidents **(Fig. 2).** A new system for reporting outcome based on predetermined criteria was also incorporated into the form.

The intent of these changes was to enable better use of the information reported on the incident reports and to assess various trends using run charts, Pareto diagrams, and other statistical methods. The more comprehensive information now available will assist in identifying the most common breakdown points in the medication administration system so that corrective interventions can be focused on these areas. If the Pareto principle that 20% of the variance causes 80% of the problems applies in this case, identifying and correcting a few of the most frequent breakdown points may prevent a large portion of the incidents. It is the taskforce's intent to collect and use this data over the next year as part of the process of ensuring the safe use of medications in the institution.

Conclusions

The continuous quality improvement approach involves an ongoing process that continues until the system is improved to a point at which further improvement is unobtainable. The prevention of medication errors and the enhancement of the medication prescribing, dispensing, and administration system is a good paradigm for the application of this process. The involvement of a multidisciplinary team as well as the users of the system is vital to the success of this approach. Ultimately, the users of the system and the patients it serves will benefit from the adoption of a continuous quality improvement philosophy to medication incidents.

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Quality Improvement in Action:

A Falls Prevention and Management Program

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IT IS PART of nursing's heritage to evaluate quality of care and institute efforts to improve it. Florence Nightingale, the founder of modern nursing, addressed issues such as "accidents, staffing, observations and documentation" in her book *Notes on Nursing,* published in 1860 (1).

The national nursing organizations, including the American Nurses Association and the National League for Nursing, have been leaders in the development of standards of practice and education, including standards for continuous evaluation of nursing care, encouraging the use of results in determining accomplishments and in identifying problems and improving services. The Department of Nursing at The Mount Sinai Hospital in New York City instituted a formal quality assurance program in 1983, although many programs of evaluation of care antedated that program.

This article describes the program of falls prevention and management within the Department of Nursing as an example of one program developed under the aegis of the quality assurance effort.

Epidemiology and Consequences Of Falls

Patient falls in hospitals occur at a regular rate and have a significant impact on the quality of patient care (2). Two percent of all patients admitted to hospitals will fall, and one out of ten will fall again (frequent fallers) (3).

Among the elderly, injuries from falls are the sixth leading cause of death in people over age 75, as well as the leading cause of injury-related deaths and a major portion of the morbidity, mortality, and social costs resulting from age-related fractures. A quarter of a million hip fractures occur in the elderly each year; the number is expected to rise to 300,000 by the year 2000. Those aged over 75 have a mortality rate from falls eight times higher than those aged 65–74, and only 50% of those who fall are alive one year later. Hip fractures are estimated to cost $8 billion annually (4).

The New York State Department of Health requires hospitals to report within 24 hours any serious adverse event resulting in patient injury or death, and any environmental or equipment hazard which threatens patient safety. The 1986 annual report of summary data from New York State revealed that 35% of incidents reported statewide were falls. There were 4,371 incidents reported, of which 1,551 were falls. By 1988, the total number of reported incidents had risen to 9,055, with 2,000 reported falls. The consequences of falls for the hospitalized patient are often serious. They include increased morbidity with increased length of stay as well as increased cost to the hospital and patient.

Using data from a system maintained by the Federation of Jewish Philanthropies Service Organization (FOJP), the Division of Management Operations Evaluation in Nursing at The Mount Sinai Hospital conducted an analysis of the severity of falls at Mount Sinai during the years 1987–89. The data was collected from a standardized form completed at the time incidents occur. A ma-

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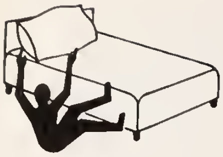


Fig. 1. Sticker identifies patient at risk for falls on Kardex, chart, intercom, and name tag on door.

jority of the falls resulted in no change in condition, with no injury. Minor injuries were recorded in about one quarter of the falls and included injuries that do not require extensive medical treatment, impair a patient's ability to function, or require an extended hospital stay. There were two deaths resulting from falls during this period, and there was a steady decrease in the number of falls resulting in a major injury (5).

Although a majority of falls result in no change in the condition of the patient, consideration must be given to the impact of a fall in terms of hospital cost and other less tangible effects. Considerable time is required of nurses and physicians for the completion of reports of patient assessment, detracting from overall unit efficiency and increasing costs. Costs may also increase if patient assessment includes the recommendation of x-ray, medication or other treatment as well as an extended hospital stay for which there is no reimbursement. Also significant are the less tangible costs related to the patient's emotional status, including the impact of fear of falling and the loss of independence. Institutional impacts include the sense of failure ex-

Assessment of Risk for Falls
Revised 1992

Level 1: All patients are assessed

Level 2: Patient at risk for falls:
Can understand instructions and ask for assistance; has one or more of the following

- Medications that increase potential for falls
- Physical assessment
  - —BP sitting/BP standing: Is there more than 20 mm Hg systolic decrease?
  - —Balance assessment: Does patient sway when standing still?
  - —Range of motion: Shows decreased ability to bend foot upward
- General weakness
- History of falls/dizziness/blackouts within last three months
- Impaired mobility: Does patient have decreased functional ability
  - —Getting in/out of bed
  - —Transferring to wheelchair/chair/commode
  - —Requiring assistive devices
  - —Ambulating
- Impaired urinary/GI function
  - —Nocturia
  - —Incontinent
- Impaired sensory function
  - —Hearing
  - —Vision
  - —Speech

Level 3: Patient at risk for falls:
Unable to understand instructions or unable or unwilling to ask for assistance or follow interventions

- Altered mental status
  - —Impaired judgment
  - —Disorientation
  - —Memory loss

Guidelines for Nursing Care—Falls
Revised 1992

Level 1: Patient assessed as not at risk for falls

- Orient patient and family to immediate environment
- Lock bed in lowest position
- Consider use of one-four siderails as appropriate
- Place call light, telephone, and bedside stand within patient's reach
- Monitor for side effects of medications that increase potential for injury
- Provide assistive devices as needed

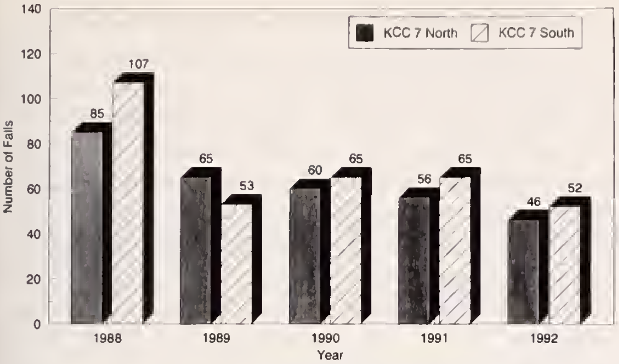
Level 2: Patient at risk for falls:
Can understand instructions and ask for assistance and is willing to comply with interventions

- All interventions above
- Label patient's Kardex, chart, intercom, and name tag on door
- Accompany patient to and from bathroom as needed
- Offer bedpan as per patient's identified voiding pattern
- Offer assistance with Activities of Daily Living
- Make appropriate referrals

Level 3: Patient at risk for falls:
Unable to consistently understand instructions; unable or unwilling to ask for assistance or follow interventions

- All interventions above
- Reassess patient's ability to understand and follow instructions as indicated
- Reorient to person, place, and time every shift and PRN as necessary
- Observe visually as indicated
- Move patients to a bed closer to nurse's station if appropriate
- Apply restraints as ordered by MD
- Offer spouse or significant other the opportunity to participate in care of the patient as appropriate

If the patient has a history of recent falls, dizziness, or blackouts, or if at least two indicators on the assessment form (left) are checked, or if one or no indicators are marked but the registered professional nurse deems it necessary, the Guidelines for Nursing Care—Falls (right) is instituted, and a request for medical assessment of the indicators noted is made.



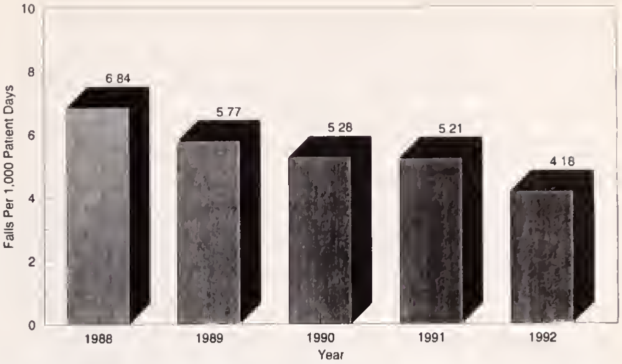


Fig. 2. Left Actual number of falls, 1988–1992, on KCC 7 North and KCC 7 South, The Mount Sinai Hospital. Fig. 3. Right Falls per 1,000 patient days, 1988–1992, in Psychiatry Division, The Mount Sinai Hospital.

perienced by the staff caring for the patient; the activities of the Social Work Department and the Patient Representative Department in counseling family and patient; the impact on the community's perception of the quality of care provided by the hospital, as well as the loss in time, money, and good will which may result from litigation brought by patients or families against the institution or health care worker. Falls are cited by the American Nurses Association as the most common reason that nurses and physicians are sued for medical negligence (4).

Falls Prevention and Management Program

In the spring of 1987, a Falls Awareness Program was initiated at Mount Sinai. A Nursing Task Force was formed to develop a comprehensive policy on the issue of patient falls whose purpose was twofold: to serve as a guide to departmental behavior in this area, and to serve as a standard which could be used in conducting studies on patient falls (6). In 1988, the task force developed and published (7) this policy statement:

> Adult patients admitted to The Mount Sinai Hospital will be assessed for the risk of falling by the Registered Nurse responsible for admitting the patient. Thereafter, an assessment will be completed by the Primary/Associate Nurse when the level of activity changes or there is a change in the patient's condition.

Also developed were a form for assessment (see **ruled box**), used each time the patient's condition or level of activity changes, or the patient is transferred within the institution, a standardized nursing care plan for patients at risk of falling, and a sticker to be affixed to the chart of those individuals judged to be at risk for falling (**Fig. 1**).

The department continued to collect raw data on the number of falls which occurred on each unit and to analyze it in relation to the time that the falls occurred, patient diagnoses, and level of activity privileges, at both the department level and specific unit level to gain insight into the possible causes of falls. Unfortunately, comparison of data by unit from year to year has proven to be extremely difficult due to the reconfiguration of units which has resulted from the construction and occupancy of a new hospital pavilion and the regrouping of patients by clinical entity.

Experience in Psychiatry. In 1988, it was observed that a large number of patients were experiencing falls on two particular psychiatric units, known as KCC 7 North and KCC 7 South. The high incidence of falls on the units was identified as being due to the first-time admission of a high concentration of geropsychiatric patients to KCC 7 South and the admission of a high concentration of geropsychiatric patients with a primary diagnosis of dementia to KCC 7 North. These two groups of patients were frequently falling, with the result that these units were experiencing one of the highest fall rates within Mount Sinai Medical Center.

Nursing leadership in psychiatry, assisted by unit quality assurance representatives, identified the problem, assessed needs, instituted a program of education for staff (both medical and nursing) and patients and significant others, and modified the system of delivery of care. Enlisting the cooperation of the senior management group within the division, a committee was formed to evaluate the clinical, environmental, and patient care systems and to recommend necessary changes to the senior management group.

Having identified the patient population at risk for falling, the following interventions were instituted: Geri chairs and Posey vests were made available to meet the needs of the patient population; nursing staff mix was modified by the addition of more licensed practical nurses and nurses aides to meet the custodial needs of patients in toileting, feeding, ambulating; and patients with like needs or problems were clustered together to make delivery of care easier as well as more economical—patients requiring close observation were placed in adjacent beds or rooms. A major educational program for all staff was also introduced by an education specialist and a clinical supervisor in nursing. Continuing feedback was a key feature of these education programs.

A system of chart review for all patients who fell, following each fall, was established to ensure that appropriate interventions were in place. In this system, the worker analyzes the circumstances surrounding the fall and identifies needed interventions. On KCC 7 North, the staff initiated toileting and ambulating schedules of 2 hours to 4 hours for patients deemed at high risk for falling. On KCC 7 South, the staff included a status report on each high-risk patient in the change-of-shift report, and close observation schedules were introduced to include not only observation of the location and condition of the patient, but also an examination of the status of the medical devices in use to assist the patient in remaining in the bed or chair.

The falls prevention program, as developed by the Nursing Falls Task Force, has been particularly effective in the Psychiatric Division. Statistics gathered for the two units are dramatic, revealing a steady decline in the number of falls from 1988 to 1992 (Fig. 2). On KCC 7 North, the total number of falls in 1988 was 85, with a steady decline to 46 in 1992. A similar decline occurred on KCC 7 South, where 107 falls were recorded in 1988 and 52 in 1992.

Equally significant has been the reduction in the rate of falls per 1000 patient days, which is a standard used in developing a statistically comparable base (see **Fig.** 3). The rate equals the number of falls from the FOJP data divided by 1000 patient days (determined from discharge statistics). As indicated, the rate in the Psychiatry Division declined from 6.84 in 1988 to 4.16 in 1992.

On an institutional basis, the falls assessment form was added to the admission assessment form to facilitate adherence to the policy that all adult patients be assessed for risk of falling at time of admission. An Interdisciplinary Task Force on Falls was also convened, with representatives from the Departments of Medicine, Geriatrics, Nursing, Pharmacy, and Rehabilitation. Among the activities to which the task force has contributed its expertise are the selection of equipment and furnishings, the offering of three educational seminars, and the assessment of devices marketed as deterrents to falls. In addition, during 1992 the Nursing Task Force on Falls achieved consensus on the definition of a fall to assist in establishing consistent data. Today, data continues to be collected as a means of measuring progress.

Summary

A departmental program for falls prevention and management, initiated in 1987, and arising out of the awareness of the economic, physical, and psychological effects of falls in hospitalized patients, has been described. Given the results outlined, there is no doubt that the efforts applied in the area of falls prevention have been extremely worthwhile in affecting major quality improvements in patient care. The benefits of the falls prevention program include a reduction in the incidence of falls as well as an increased awareness by staff, patients, and families of the importance of monitoring patients at risk for falls.

Acknowledgments

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Research in the Hospital Setting on Human Subjects

Protecting the Patient and the Institution

Ruth Scheuer, RN, DrPh, JD

Abstract

A hospital's institutional review board is charged with the responsibility of fully protecting the rights of research subjects. In doing so, the board establishes that research protocols are based on sound scientific principles, that benefits to research subjects outweigh the risks, and that the subject's consent is informed and not coerced. Although it has been argued that risk management has no role in the activities of such boards, the literature indicates that risk management and quality assurance principles apply to all areas of the institution, including the activities of the board. The institution must ensure that its researchers and board members are as fully protected as possible from civil and criminal liability and that the integrity of those conducting the research is established and maintained. The institution must also provide sufficient support for the board to conduct its reviews and educate the research community and board members on current and evolving laws and regulations governing human research. Risk prevention and quality assurance strategies should recognize the rights of the research subject as paramount while protecting the institution, its researchers, and the community served.

The Nuremberg Code of 1949 and the Declarations of Helsinki in 1964 set guidelines to monitor and define the parameters under which research on humans could be conducted. Not until 1966 did the United States Government establish further guidelines, under the auspices of the Public Health Service, for the protection of human subject research (1–3).

In 1966 Beecher, in an article in the *New England Journal of Medicine,* cited 22 examples of studies which were unethical or of questionable ethics and of investigators who had risked "the health or the life of their subjects" and whose protocols involved a flagrant disregard of the welfare of their research subjects (4–6). Beecher's study and other studies of the conduct of research on the general population and, especially, on those more vulnerable to abuse, e.g., those who were poor, members of a racial minority, the elderly, the mentally incompetent, and prisoners, showed that researchers failed to adequately protect their research subjects in the absence of standards to ensure adequate safeguards and an informed consent (2, 7).

In 1974, the National Research Act became law, requiring that any entity applying for a federal grant to fund behavioral or biomedical research must provide a written "assurance" (8) of the establishment of an institutional review board (IRB) charged with the task of reviewing all research conducted on human subjects (2, 6, 9). The rules which would govern research involving human subjects, whether the research was being funded in whole or in part by the federal government, were promulgated in the Code of Federal Regulations in 1978 (2, 10, 11).

In 1981, the regulations were expanded to require an IRB to review all research involving

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products regulated by the Food and Drug Administration (FDA), regardless of the research funding source, the status of the research subjects, or the research setting. Therefore, a private practitioner conducting research in his or her office must also obtain IRB approval. The IRB could be one created by a health facility, a state or local government, or the research sponsor (hereinafter the "sponsor") (12).

In 1987 and then in 1991, the FDA published regulations allowing broader and earlier use of experimental drugs, so that desperately ill and dying patients could receive the benefits of such drugs far earlier than was permitted before (13).

Regulations of the Department of Health and Human Services (DHHS) and the National Institutes of Health (NIH), as well as regulations of the FDA, set IRB requirements. The governmental agencies' regulations apply to studies involving investigational drugs and devices, whether or not they are funded by the DHHS (14).

Federal regulations provide guidelines by which IRBs must operate and also specifically require that the "parent institution is presumed to be responsible for the operation of an IRB, and the FDA . . . will ordinarily direct any administrative action . . . against the institution." The IRB, therefore, is the "reviewing body, which is acting on behalf of the institution and it is the institution which bears ultimate responsibility for the acts of the IRB" (1).

Hospitals and university-affiliated medical centers have historically been at the forefront of breakthroughs affecting the diagnosis and treatment of diseases and their manifestations. It is the medical center (also referred to below as the "institution") with which the pharmaceutical houses or other sponsors form their alliances in order to test drugs or devices they hope to market (1). Each of the parties involved in the conduct of research and its oversight must understand the rights, duties, and risks inherent in such activities. Failure of the institution to recognize the significant risk management issues associated with such research and failure of the institution to protect its officers and directors, employees, researchers, and IRB members could result in civil and criminal liability (1, 15).

The IRB serves to initially approve and continually review (16) all research involving human subjects to insure that ethical norms are met and that the research protocol provides an acceptable scientific design involving competent investigators whose research has been reviewed and approved by their superiors or peers. The research must involve a balance of risks and benefits in which the benefits outweigh the risks; the patient has given fully informed consent; the participating subjects are not recruited or obtained through coercion; and special consideration is given to populations considered at greater risk for abuse, including the mentally ill, infirm, demented, prisoners, children, fetuses, and pregnant women (2, 6, 17).

If the IRB fails to fulfill its responsibilities, sanctions could be imposed on the institution or its researchers which might cause the research sponsor or the federal government to decrease or eliminate funds, which could in turn result in the loss of institutional operating research funds; difficulty attracting respected investigators, teachers, students, and clinicians; loss of respect and prestige; and loss of sponsors for future research (1).

The purpose of this article is to outline selected areas of exposure to an institution conducting research involving human subjects and to provide suggestions for limiting such exposure.

Insurance Issues and Contract Provisions

By the time a clinical investigator brings a research proposal to the IRB, many hours will have been spent on defining the parameters of the protocol, the process of patient selection, and the research methodology, but very little, if any, consideration will have been given to the legal issues which define the contractual rights and obligations of the various parties. Defining these rights and obligations at the time the parties are negotiating and before the sponsor and institution finalize the relationship is critical. The defense of any legal action is complicated by the nature of the relationship within which the sponsor writes the protocol and drafts the contract language, the IRB approves the protocol, and the institution provides the staff who will direct the research as well as the patients who will participate in the research (15).

Therefore, part of the responsibility of risk management is to insure that the terms and the conditions of the contract are reviewed in a timely manner, and that the provisions do not make the institution the bearer of any risk or obligation which should be borne by the sponsor.

Institutional policy should mandate that no agreement may be executed on behalf of the institution unless specified conditions prescribed by the institution are met. In the event of any substantial deviation from the established parameters, the institution, through its legal counsel and administration, has the obligation to negotiate disputed contract terms with the sponsor on a timely basis without jeopardizing the research by causing unnecessary delay. Researchers who enter into outside agreements not approved by the institution should be notified that they risk incurring personal liability if found to be acting outside the scope of their employment and, therefore, might not be indemnified for unauthorized acts (2). Nevertheless, to the extent that the researcher has apparent authority to bind an institution, the institution may be legally bound by the contracts executed by its researchers.

Unfortunately, it is routine for some clinical trials to be conducted in the absence of proof of adequate insurance coverage by the sponsor. Therefore, it is critical that the institution delineate the scope and extent of the insurance required of the sponsor, as well as all indemnification provisions (15).

Ideally, there should be one written contract between the sponsor, the researcher, and the institution and it should incorporate by reference the agreement between the investigator and the sponsor. The researcher must understand that the contract generally contains specifications of the study (number of patients to be enrolled, time frame for the study, payment for conducting the study, and so on). Although the needs of each institution will differ, the contract between the institution and the sponsor should specify, at a minimum, that the sponsor must maintain comprehensive general liability insurance. The sponsor must provide the institution with insurance which includes contractual and product liability as well as personal and bodily injury and broad-form property damage coverage.

The sponsor should also agree, as part of the contract, to indemnify the institution, its trustees, officers, directors, employees, students, and agents from any liability, damage, costs, and expenses, including reasonable attorneys' fees, settlements and judgments for personal injury (including death to any person), and damage to property which results from activities to be carried out pursuant to the protocol. The notice or reporting requirements of a claim or suit must be reasonable. The indemnification must survive the term of the contract and be in full force and effect until all applicable statutes of limitations have expired. This includes actions in malpractice, negligence, personal injury, product liability, and contract. Sponsors, however, do not generally indemnify the institution for the negligence of the institution or its employees or any violation by the institution of state or federal statute. In addition, strict adherence to a research protocol will not shield the researcher from civil liability if procedures are performed negligently (2).

In addition to insurance and indemnification provisions, other terms and conditions include conditions under which the sponsor may use the institution's and the researchers' names in any advertisement or promotional material, and under which the researcher may publish or communicate the results of the research; maintenance of confidentiality related to privileged or proprietary information; and patent and invention rights.

The sponsor must agree to indemnify and hold the institution harmless from all liability, costs, and expenses sustained as a result of any claim arising out of the performance of the contract, and must warrant that (a) the drug or device under investigation has a valid and current Investigational New Drug (IND) application (18) or an Investigational Device Exemption (IDE) application (19) on file with the FDA (20); without such an application no clinical investigation can legally take place; (b) the researcher will be promptly provided with all pertinent data so that the IRB and researcher can fulfill their collective responsibility in protecting research subjects from all unreasonable risks and ensure adequacy of informed consent; (c) the product being studied is safe when used in accord with the prescribed protocol; (d) the sponsor is the sole owner of the rights and title of the product furnished to the institution, the product infringes no patent, copyright, or trade secret, and the sponsor has the right to authorize the study which is the subject of the contract. The terms under which either party may terminate a clinical trial must be included, and the law governing the contract should be the law of the state in which the institution is located.

The IRB Review Process

Once the research protocol has been established by the sponsor and researcher, the protocol will be submitted to the IRB for its review.

The IRB must have a minimum of five members with varying backgrounds sufficiently qualified to safeguard the rights and welfare of human subjects. The members must be able to determine whether the proposed research is acceptable in terms of the institution's commitments, policies, regulations, applicable law, and standards of professional conduct and practice. The IRB should include at least one member whose primary concerns are nonscientific, and one member not otherwise affiliated with the institution (21). IRB members must be well versed in the federal regulations applicable to research on humans. They must review each protocol in great depth to determine the risks to the patient and, to the extent possible, protect the patient from injury.

Potential liability for IRBs arises under several theories. In addition to being subject to sanctions for failure to follow federal guidelines, the IRB may be subject to suits by research subjects alleging that the IRB negligently discharged its duties in protecting research subjects, leading to injuries which would not have occurred if a reasonable person confronted with the same information had placed conditions on the research to prevent injury (1).

Informed Consent. Negligence could also be alleged for approving consent forms which do not legally rise to the level of truly informed consent, thus rendering the subject unable to comprehend the nature of the research or the risks, benefits, and alternatives (15).

In addition to federal regulations, common law also contributes to the definition of "informed" consent. In one case involving a study of the efficacy of diethylstilbesterol (DES) in preventing miscarriages, the plaintiffs alleged that although the relationship between DES and cancer was known at the time of the study, the defendants never informed the subjects of the risk. The court found that the sponsor and the institution had an affirmative duty to inform research subjects of the risk involved in DES treatment when they knew or should have known of the relationship between DES and cancer (22).

In another case, in which the plaintiff had participated in a nontherapeutic diving research experiment and had signed a consent apprising him of the known and possible unknown risks, he alleged that he suffered organic brain damage, a risk not noted. The court held that a consent in the nontherapeutic context required a higher degree of risk disclosure than did state law, which used a standard applicable to health care treatment. This stricter standard required written and verbal disclosure of all reasonably foreseeable risks (23).

The Supreme Court of California has also ruled that the failure of a physician to disclose his research and economic interests in obtaining the patient's cells, which were to be marketed for a considerable profit, before obtaining consent to the medical procedures used to extract the cells created a cause of action for breach of the California informed consent/disclosure requirement (24).

Scientific design can also affect the process of consent; if the design is so poor that no generalized knowledge will result, the benefits of the study may be minimal or nonexistent, precluding the subject from making an informed consent (2, 15).

The FDA and others have identified a number of problems relating to the adequacy of the informed consent (6, 25–30), including failure to explain technical language, to state that the drug or device is experimental, and to completely describe all procedures and purposes of the research; for example, including only those purposes that are beneficial; employing overly optimistic wording or tone; for example, using terms such as "product extensively and safely used elsewhere"; inadequately describing treatment alternatives or risks and benefits.

Protocol Design. Research on the work of IRBs suggests numerous risk-management issues. Goldman (31) studied 22 institutions, reviewing identical anesthesia and oncology protocols, each posing serious ethical issues or containing flaws in scientific design or incomplete consent forms. Goldman found inconsistencies in the application of ethical, methodologic, and informed consent requirements among the IRBs studied. Although inconsistencies might be expected because different IRBs are bound to approach their tasks differently, the evidence suggested that some IRBs were not protecting patients adequately, either by not providing adequate safeguards during the research itself or by not meeting acceptable guidelines for informed consent, and that a more careful review of protocols would result in improved decision making related to approval of research protocols.

Grodin et al. reported on problems ignored by IRB reviews (32). These included protocols with an inadequate scientific database obscuring the rationale, justification, or necessity for subjecting the patient to any risk, discrepancies between the way the study was perceived by the principal investigator and the manner in which the protocol was written, conflict between hospital policy and clinical policy not resolved by the study design, and excessive invasive diagnostic medical procedures outlined in the protocol.

Other Potential Causes of Liability. Other deficiencies related to IRB functions include incomplete or missing records; inadequate written procedures; lack of a quorum at meetings (defined as more than half the members, including one member whose primary concerns are nonscientific); and inadequate continuing review of research protocols (33) or performing a review so cursory that preventable injuries to subjects occur because of the absence of adequate safeguards (1).

Despite all the potential causes of liability, Holder has indicated (ref. 25 at 23.99) that as far as she can determine, there has never been a suit filed against IRB members as a group for "negligent approval of a protocol."

Strategies for Improving IRB Review. Many of the potential problems noted in researchers' observations of IRBs could be resolved prior to formal presentation of a protocol. Others could be resolved during the formal IRB review. Risk management strategies can be used to great advantage to avoid unnecessary delays in revising protocols and consent statements to meet federal regulations (34). Some examples:

Developing ongoing educational programs for those engaged in research activities which emphasize the specific requirements mandated under federal regulations and stress the rules and procedures governing human subject review. Ongoing educational programs would allow the investigator to understand and, therefore, be in a better position to respond to the demands of the IRB review (34, 35).

Providing an investigators' handbook with written policies and procedures defining the parameters for approval of all research protocols, including at a minimum a description of the mandate of the IRB; guidelines defining a research endeavor, including specific areas the protocol must address to be acceptable for IRB review; submission requirements to the IRB, including time frames; a check list incorporating the requisite elements which must be included in all informed consents (26); and policies and procedures that apply in special circumstances, such as research involving minors, prisoners, fetal tissue, or pregnant subjects (1–7).

Developing a lexicon of key technical words or phrases that translate the language that appears in a significant number of research protocols into terms understandable by a lay person, including such terms as "placebo," "randomization," "double blind," "catheterization."

Assigning one or two IRB members as primary (and secondary) reviewers to review a protocol in depth prior to presentation at the full IRB meeting, thus allowing assigned IRB members to have informal discussion with the researchers that would inform them of any problems identified, whether in research design or in aspects of the informed consent statement, and would give researchers an opportunity to correct the problems noted prior to formal IRB review.

Educating IRB members that all the risks as well as the benefits in the protocol must be mirrored in the informed consent. Thus they should give special attention to reviewing those areas of the protocol that address risks as well as to identifying other unique requirements, such as special warnings, for example the risk of pregnancy, and special precautions such as whether women subjects will be required to take a pregnancy test prior to entering the study.

Establishing IRB parameters for continuing review at the time of initial approval of a protocol. Federal regulations require that frequency of review be related to degree of risk and be undertaken at least annually. The IRB should make it clear that researchers who do not provide progress reports in a timely fashion may face withdrawal of IRB approval and termination of the research (33). In addition, when the research has been completed, a final report of the findings should be submitted to the IRB. This includes protocols completed in less than one year.

Ensuring a majority of IRB members at meetings by scheduling meetings in advance and delivering protocols to members a minimum of 10 days prior to the meeting to allow careful review of all protocols and informed consent forms.

Finally, the legal or other relevant department of an institution may be asked to review a protocol to determine whether it conflicts with institutional policy or state or federal law, or whether performance of the research would present a substantially unacceptable risk to the institution far outweighing any benefit to the patient.

Although the IRB is not expected to provide on-site monitoring of performance of research, it has the authority to monitor performance, rescind approval of protocols, prohibit further research and notify the institution, the funding agency, and federal and state authorities where breaches of research protocol occur. Therefore, to the extent possible, the IRB should develop ways to recognize and avoid misuse or abuse by a researcher. Stricter oversight by an IRB may, therefore, be necessary where "the research involved is especially risky; the research population is vulnerable to poorly constructed consents; and the researcher is prone to obtain poor consents" (36).

Non-IRB-Approved Research on Human Subjects. Individual departments, through their chairpersons, must also ensure that no research on humans not approved by the IRB is being performed. Even if the IRB is unaware that a study is being conducted, a rare situation, the IRB and the institution may be held liable for injuries to subjects resulting from unreviewed or unapproved research, where the institution knew or should have known that the research was being conducted or where the institution failed to guard against evasion of the review process. One way to attempt to ferret out unapproved research projects is for the comptroller or financial officer of an institution receiving monies from outside sources to notify the IRB of grants involving research on human subjects. The IRB office can determine if a concomitant proposal has been submitted, reviewed, and approved, thus creating a check-and-balance system.

The penalties for conducting unauthorized research are severe and if unapproved research is being conducted, swift action must be taken by the institution. Sanctions can subject a researcher to "(1) suspension; (2) termination; (3) denial of laboratory space, subjects or the resources of the facility; (4) denial of a legal defense for acting outside the scope of employment; (5) licensure board sanction; (6) denial of affiliation research title in publications; and (7) the possibility that research materials may be confiscated or destroyed" (2).

Scientific Misconduct

Each institution is required by federal regulations to have a policy addressing scientific misconduct in research (37). Scientific misconduct includes fabrication, falsification, plagiarism, or other practices that seriously deviate from those practices commonly accepted within the scientific community for the purpose of conducting or reporting on research (38). Scientific misconduct does not, however, include honest error or difference in interpretation or judgment (39).

The U.S. Public Health Service (PHS) guidelines suggest that the procedures for determining the existence of fraud or misconduct generally involve four stages: (a) an inquiry that determines whether an allegation of misconduct warrants any further investigation, (b) when warranted, an investigation that collects and examines all the evidence, (c) a formal finding, and (d) appropriate disposition of the matter (37).

A policy relating to scientific misconduct should define the responsibility of the principal investigator to supervise junior researchers and of the department chairpersons to oversee all research conducted by members of their department; how research data is to be collected, stored, and retained; the rules and regulations governing authorship and publication practices; and the processes for handling allegations of misconduct in research, including protection for the whistle blower; the initial inquiry process; how findings are to be reported and to whom; the investigatory phase; the rights of the subject of the investigation to a full and fair hearing; confidentiality of the allegations, to protect the reputation of the accused until misconduct is reasonably certain; provisions for including outside expert consultation to insure faculty objectivity; ways to restore the reputation of the investigator if the allegations are found to be frivolous; reporting of findings and recommendations; appeal process; final review by the governing board of institutions; disciplinary actions and sanctions; and procedures where research occurs at or involves an employee of an affiliated institution (37, 40).

The policy must indicate when notification of appropriate state and federal agencies, including the Office for the Protection of Research Risk and the Office of Research Integrity, and notification of the sponsor must be undertaken if, in the course of an investigation, findings suggest an immediate health hazard; an immediate need to protect state or federal funds or equipment; an immediate need to protect the interests of persons making allegations, the accused, his or her co-investigators, associates, or colleagues; probability that the allegation will be reported to the public; reasonable indication of possible criminal violations; and whether, where applicable, the research will be terminated prior to completion (39, 41).

Conflicts of Interest

Modern technology now allows new basic raw materials to be developed for use in clinical laboratories and the rapid development of products with commercial value. This technology has led to increased cooperative efforts between institutions and industry to serve the interests and meet the needs of the general public and the research community. However, this has also led to growing pressure on scientists, institutions in which research is conducted, and the federal government (frequently a partner with industry and the institution supporting research efforts) to define when and under what circumstances a conflict of interest may or does exist as a result of one or more parties benefiting financially from the outcome of the research being conducted. The judgment of the researcher and, therefore, the scientific integrity of the research may be affected where the institution or the researcher has a vested interest (either through stock holdings, consulting arrangements, or other types of employment) in the development of the product (42).

Although most universities have policies governing conflicts of interest, hospitals in which research is being conducted may not have policies covering a perceived or potential conflict of interest involving research (43). It is important for the IRB to recognize that such a policy will be crucial in avoiding even the appearance of impropriety and the resulting negative public exposure, which could lead to discrediting of research findings and possible civil liability. At a minimum, a policy on conflicts of interest should require disclosure by every member of the research team of any relationship with the sponsor of the research, whether as a consultant or in any other capacity (stock ownership, equity interests, patent-licensing arrangements, or any other association outside expected participation in the proposed research protocol) (42).

Disclosure by the researcher of any potential conflicts of interest should be included as part of the required materials the IRB receives for review and approval of all protocols. In addition, Healy et al. (42) include a requirement for annual reports by the investigation of participation in educational activities or other research studies supported by the sponsor, scientific consulting activities to the sponsor, including those unrelated to the current research and in the absence of any financial interest or compensation, and financial interest in the sponsor over which the investigator had no control (mutual funds, blind trusts).

The aim of an institutional policy on conflicts of interest which will guide the IRB should be to develop systematic and clear criteria informing investigators of the conditions requiring disclosure and to resolve real or potential conflicts of interest. Implementation of the policy should assist the IRB in maintaining the integrity of research and protecting its subjects.

Conclusion

The mandate of the IRB is to ensure that patients or other volunteers are protected and informed as fully as possible when participating in clinical or other studies as research subjects. Historically, the concept of risk management has not been focused on the IRB. Nevertheless, some risk management strategies apply not only to patient treatment but to clinical research as well.

The institution must, through its IRB, ensure the integrity of the researcher and the research to protect the rights of those participating as well as the reputation of the institution and its employees and agents. The institution must also ensure that it, its researchers, and its IRB members are protected as fully as is possible from civil and criminal liability.

The institution must also be aware that if the IRB is to effectively fulfill its mandate, it must be provided with the funds and staff support required to conduct its reviews and educate the research community and IRB members on current and evolving laws and regulations governing human subject research as well as the ethical considerations which form the basis for all IRB decision-making.

Risk management strategies should not be seen as an obstacle to this process, but should be viewed as a tool through which decisions are reached which will protect the research subject, encourage new frontiers of research, and protect the interests of the institution and the community that it serves.

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The Consumer Survey Review Process:

A Pathway to Quality

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Abstract

This paper describes the consumer survey review process (CSRP), a vehicle for continuous improvement of patient care quality at The Mount Sinai Hospital in New York City. Following a historical sketch of the events which led to its establishment at Mount Sinai, we then describe the instrument used to elicit patients' rating of service delivery, the Consumer Survey, and show how it meets the changing requirements of those who use it. Next, we explain the role and functioning of the management group that most directly translates the patient satisfaction data into action, the Consumer Survey Review Group. Finally, we discuss implications of Mount Sinai's consumer survey review process for managing quality in health care.

THERE IS much talk today in the health care field about the importance of "managing quality" (1, 2). Whether the conversation is about total quality management, continuous quality improvement, patient-focused care, patient-centered care, or any other version of quality management, the emphasis is on building quality into the fabric of the organization through empowering teams to find ever better ways of meeting customer—that is, patient—requirements.

This paper describes a process which uses feedback from patients to continuously improve the quality of hospital services. At The Mount Sinai Hospital in New York City, the process is known as the consumer survey review process (CSRP). The core elements of this process are (a) a commitment to continuous quality improvement; (b) a quarterly survey of patient satisfaction using a carefully designed survey instrument; and (c) ongoing, active management involvement in the process through learning and action.

Background

In the early 1980s, a group of managers and clinicians met to create a new patient satisfaction survey for Mount Sinai. In doing so, these managers sought to change an existing process that was not only deficient in terms of the statistical data produced, but also tended to focus primarily on negative findings. Less than 20% of patients returned the original questionnaires they were given prior to their discharge. Managers would receive the results for their areas only, often with low ratings circled in red with a note from a superior asking for an explanation—in writing.

The context for the meeting to change this system has been described elsewhere (3). Suffice it to say that Mount Sinai was embarking on an attempt to have its reputation for caring become equal to its reputation for curing. Although patient satisfaction with the technological and clinical aspects of medical care was known to be high, the collective perception was that psychosocial aspects of the patient experience could be improved. It was obvious that if changes were going to be made, reliable and valid patient feedback was essential.

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The group that had the task of designing a new instrument to measure patient satisfaction consisted of representatives from the Departments of Medicine and Nursing as well as from front line hospital clinical and support service areas. Social scientists from the Department of Community Medicine assisted in the task. Since the process of questionnaire design has also been described elsewhere (4), we will not go into detail here. However, the management group was given the freedom to create the methodology for assessing patient satisfaction with services along with the responsibility for ownership of the process. This produced a survey instrument that managers felt comfortable with and confident in, and a process that from inception was highly professional and participative.

The decision by the group to continue to meet regularly after the new patient survey was designed and implemented led to the establishment of the consumer survey review group (CSRG). From its inception, this review group has been a vehicle for collegial sharing of data and ideas. The intention was to break from the former pattern of seeing only data that pertained directly to one's own department or area of responsibility, and to change the focus of management attention from negative to positive. The CSRG's original members saw the value of learning in a collegial setting, interpreting the results by looking at patterns that crossed departmental boundaries. This approach was a natural one for line managers to take, since it squares with day-to-day reality. Delivering patient care requires coordination of services. The performance of one department can and does influence the ability of another to perform its function. Consumer ratings of hospital services, therefore, had to be interpreted in an interdepartmental and interdisciplinary fashion.

Goals of the Mount Sinai Review Process

For almost a decade, the various elements that comprise the consumer survey review process have worked toward achieving the following goals:

- To promote awareness throughout the institution of Mount Sinai's commitment to continuously improve the quality of patient care as perceived by our patients.
- To stimulate a spirit of inquiry among managers into the factors that influence patients' ratings of their satisfaction with hospital services.
- To create opportunities for managers, individually and collectively, to deepen their understanding of patient satisfaction with hospital care, and to plan actions that lead to improvements in service delivery and the quality of patient care.
- To provide a reliable mechanism for evaluating actions initiated by managers to improve the quality of service delivery.

Core Elements: Continuous Improvement. Most aspects of the consumer survey review process have undergone change over the years in order to produce a more effective vehicle for bringing about improvement in the quality of hospital services. Although the original notion of satisfaction as a measure of how patients perceive both technical and humanistic aspects of care has been constant over the years, the flexibility of the survey instrument has allowed us to assess a broader range of patient experiences. In addition, several departments have created satisfaction surveys tailored to the needs of their specific patient population.

The responsibility for implementing the patient survey and for insuring that all phases of data collection and data analysis meet professional standards is the responsibility of the Mount Sinai Survey Center, which is staffed by experts in action-oriented research design and statistical analysis.

The past decade has seen improvement in statistical methods for both validating the survey instrument and analyzing the results. Attention has been given to precision in sampling, understanding response patterns, measuring reliability, and employing multivariate statistical techniques. Increased access to hospital databases has allowed us to incorporate a variety of relevant demographic variables in the analysis. Most recently, we have shortened the turn-around time between the end of the survey period and the distribution of results. We can now send managers the results of the survey soon after the completion of the data collection, which means that their own response to the results can now begin much sooner than previously.

At the outset of the CSRP, the data went to a small number of managers. Over the years, the list of those receiving copies of the data has lengthened and become more inclusive. Awareness of the data is widespread among upper management and the quality assurance staff. The Patient Care Committee of the Board of Trustees receives a hard copy and a verbal report on the data. Articles about the work of the CSRG and reports of survey results have been publicized in the institution's internal media and have been incorporated into various management training and development programs.

Core Elements: The Consumer Survey. The consumer survey (CS) is one of the key elements of the review process. It provides a quantitative, empirical, and objective ground on which to base continuous evaluation and improvement in service delivery and patient care. The survey is a quarterly telephone survey of recently discharged inpatients. Consumer selection begins the fourth week of the first month of each quarter and continues for approximately six weeks. One thousand patients are randomly selected from the hospitals' admission/discharge/transfer (ADT) information system. Patients from psychiatric services, newborns, those with a length of stay less than two days, and those without a phone number are excluded from the sample. All selected patients are contacted by a telemarketing firm within two weeks after discharge. Respondents can be patients or significant others who have knowledge of the hospital experience. Each respondent is asked a series of 60 to 70 questions related to various aspects of their hospital stay; admitting, blood drawing, business office, food, housekeeping, medical care, nursing care, social work, transportation, X-ray, overall comfort, courtesy and security, and hospital experience. Each question has a four-point rating scale (poor, fair, good, excellent).

On average, 75% of the 1000 randomly selected patients are successfully contacted and interviewed. The bulk of the remaining 25%, the nonrespondents, are either not reached after six successive, staggered telephone calls, or have an incorrect phone number in the ADT information system. Very few, usually less than 2%, refuse to answer the survey questionnaire once contacted. In fact, patients are universally and overwhelmingly appreciative of Mount Sinai's interest in their satisfaction.

The structure and process of the consumer survey is best understood in relation to the integrity, flexibility and responsiveness of the survey to both consumers and patients.

Integrity: The integrity of the data, methods, and reports is the cornerstone of the survey. A great deal of time and effort is devoted to ensuring that all aspects of the survey are based on sound empirical methods. The integrity of the raw data and the process of sample collection are continuously monitored. The most recent change in raw data collection was the direct link to the hospital's new ADT information system. Data related to the entire patient population is now immediately accessible for sampling and secondary data analysis. Because of the change in data collection, statistical comparisons were performed to ensure the integrity and continuity of the sample.

The instrument, the 60–70 item questionnaire, is also the subject of continuous critical review and analysis. Many of the items cluster to form coherent units of analysis (factors). Factor-level scores suggest a well-structured instrument and increase the reliability of results. In addition, various analyses have demonstrated that the questionnaire has a good deal of internal consistency and validity. Changes to the fundamental structure of the questionnaire (item rewording, inclusion, deletion) are subjected to a rigorous set of statistical and data analytic procedures. For example, when the Department of Nursing proposed a new set of nursing items, the Survey Center performed a separate study to describe the statistical properties of the proposed items and to review their impact on the overall survey instrument. The Survey Center is currently exploring the impact of questionnaire integrity associated with replacing the four-point scale with a five-point scale using the terms "excellent," "very good," "good," "fair," and "poor." The patient satisfaction literature and the results of a pilot test have demonstrated a better distribution and increased reliability using a five-point Likert scale.

Flexibility: Although data integrity is necessary, it is not sufficient to ensure that the data will be useful. Useful data must be flexible. The flexibility of the survey data set is grounded in the level, breadth, and mechanism of data collection. For example:

Both micro and macro organizational analysis are supported by consumer survey data collected at the level of the nursing unit, a primary organizational element. Hospitalwide service trends are described, and secondary analysis provides operational managers with the department-specific feedback necessary to effectuate corrective action planning.

The patient-specific nature of the data enables the Survey Center to work collaboratively with managers in identifying patient subgroups for special analysis. The opening of a kosher kitchen was accompanied by a special joint project between the Survey Center and Food Services Department. Food Services was able to identify patients on a kosher diet. This specialized data set was merged with the survey data to evaluate the impact of the kosher kitchen on patients with kosher diets.

Both specialized and natural patient subgroups can be identified. The breadth of routinely collected ancillary data supports the exploration of satisfaction in naturally occurring patient subgroups—sex, age, diagnosis, hospital service, and so forth. The supporting data set of patient demographic and hospital-related variables is necessary if patient satisfaction is to be described in terms useful to the organization; for example, scores on admission by point of admission, or female patient satisfaction by service category.

The mechanism by which data is collected must be inherently flexible in order to understand, as well as describe, patient satisfaction. A portion of the survey instrument is reserved for "additional" questions. Past surveys have had additional questions related to the Business Office, to Public Affairs/Marketing, and to the exploration of patient health as it relates to satisfaction. Any set of additional questions is attached to the end of the survey instrument for one quarterly survey. Their placement ensures that patients are asked a core set of patient satisfaction questions before additional questions are introduced. This mechanism preserves the integrity of the longitudinal patient satisfaction data set while enabling the survey to remain current and responsive.

Responsiveness: As a benchmark for continuous quality improvement in a dynamic health care delivery system, the survey must respond effectively and efficiently to a changing environment. Over the years, the survey has adapted to the construction of new hospital buildings, expansion of services, modification of unit and service classifications, new institutional leadership, departmental reorganizations, and a new hospitalwide information system. It is the responsibility of the Survey Center to understand the organizational changes which have a direct or indirect impact on the survey and to interpret those changes to the Consumer Survey Review Group.

The review group, in turn, must ensure that the data and reports of the survey meet their needs. The research group has, in addition, stimulated the redefinition of the function of the survey by continually testing hypotheses, requesting secondary data analyses and manipulations, outlining customized reporting needs, and using survey data in various aspects of organizational development. For example, in addition to the hospitalwide quarterly consumer survey report, a number of departments receive customized reports to meet focused and specialized applications of survey data. It is through this process of collaboration between the Survey Center and the Consumer Survey Review Group, and a mutual commitment to quality through service, that the survey data continue to offer reliable and valid measures of service delivery and provide an impetus for continuous quality improvement.

Core Elements: Creating a Climate for Dialog, Collaboration, and Problem Solving. The consumer survey review process is designed to meet the data needs of our internal customers, the hospital managers, as the institution strives to provide the highest quality of care to our external customers, the patients. In fact, hospital managers are the primary end-users of the review process, and understanding their evolving information requirements is a vital service goal of the Survey Center.

At the core of this process is the ongoing dialog between the Survey Center and the administrative and clinical managers in departments throughout the medical center. Administrators and clinicians must thoroughly understand what is regularly done. But more than that, they must be familiar with what can be done. They must know the basics of the ongoing process as well as take an active role in designing special studies and secondary analysis. Meeting with them regularly to discuss the survey and elicit their ideas about additional survey questions provides an essential grounding for the entire review process.

The offices of the Survey Center are open at all times to managers who wish to have guided access to the database for purposes of testing hypotheses and creating specialized data analyses for planning or for presentations involving patient satisfaction data. On these occasions, the Survey Center staff acts as their consultants. This is a critical aspect of the vital link between the patients, local hospital management, and the entire medical center community. The members of the review group have positions of significant responsibility in the medical center and from those positions are able to influence how resources of their departments are utilized. Because of their institutional roles, they are also in a position to affect norms and behaviors. In this capacity they are important cultural change agents in the medical center.

Consumer-centeredness is built into the process by which the survey is updated. For example, when the Department of Finance suggested that the current set of questions related to the services of their department needed to be modified, the first step was to design a set of follow-up, or probing, questions to be used along with the standard questions. The data provided by patients to these follow-up questions will form the basis of any change that Finance wishes to make to the existing set of questions. Moreover, the information obtained from patients helped management better utilize the current data set.

Open communication during meetings of the review group is encouraged to foster mutual learning, respect, and collaboration. Merely knowing what the current ratings are is insufficient for understanding how organizational patterns of service delivery can be changed to meet the needs of patients and their families. The discussions that take place within the group help foster understanding and encourage collaboration. Members review problematic as well as positive patient feedback. They describe administrative and clinical activities that may have influenced the scores. They share information that might not otherwise be known outside their areas. Often, this dynamic leads to collaborative thinking, problem solving, and action planning.

Willingness to share openly is fostered by the belief that health care service delivery is, and should be, a fundamentally interdepartmental and interdisciplinary activity. Quality, and especially continuous quality improvement, is the result of ongoing cooperation and collaboration between all constituencies, not the single effort of one person or department. This is a norm that has been accepted by the group in theory and practice. Consumer survey results for all administrative and clinical areas are openly reviewed and presented in an institutional report. The attempt is to foster an environment in which the survey provides reliable patient feedback on service delivery and not simply ratings for a single department.

As an internal benchmark, the data provide the review group with timely, continuous, and reliable feedback on an important dimension of service delivery. The longitudinal nature of the survey data set and report package enables the review group to monitor change in service delivery over time to promote positive and arrest negative trends. In addition, the impact of both foreseen and unforeseen organizational changes on patient satisfaction and reporting can be evaluated.

As raw material, the data set provides the review group with a powerful and flexible management tool. Managers use this raw data in a number of innovative ways. Some managers share the data with line staff as a means of promoting team building, morale, and consumer-centered service delivery. Others use the survey data to guide the effective and efficient reallocation of internal resources.

Active participation means accepting responsibility for the process. This is referred to as ownership and can be observed when managers initiate secondary analysis of the data or request special studies. When a manager expresses an interest in conducting a special study, for example of how a new program or unique event will affect patient satisfaction, he or she will work in partnership with the Survey Center staff. The Survey Center does not merely respond to managers' requests. Both parties take responsibility, and an agreement is struck which assigns tasks to both. For example, the Survey Center may translate the question into a formulation that is actionable and conduct the analysis, while the department may do a significant part of the data collection, or some other set of tasks. The point is that the process requires active participation and partnership.

Survey Center staff participate actively in this process of continuous improvement by seeking feedback from review group members on the clarity and relevance of the reporting format and on issues that require elaboration in special studies, secondary analysis, and supplemental questions. In addition, staff of the Survey Center engage in national benchmarking and networking to ensure that the methods and techniques employed are state-of-the-art.

Conclusion

The CSRP keeps the institution focused on the patient's point of view. Consumer survey data are reviewed at the highest levels and are distributed widely. Through the operation of the consumer survey review group, data received from patients is translated into initiatives for system improvement. Beyond this immediate impact, the review process promotes a climate of inquiry and learning which has been identified as one of the more important characteristics of a high-performing and quality-centered organization. The quarterly data are not simply regarded as signs of success or failure—a short-term mentality which stifles initiative and impedes learning. Trends signify how departments are faring in producing high-quality patient services. Trending also prevents erroneous comparisons between unlike service areas. The review process itself fosters learning. Data are shared by managers in a neutral forum. Open discussion of changes in scores and the experience of brainstorming together promotes a sense of shared mission and reinforces the essential interdependence of hospital services. In this climate, all data—favorable or unfavorable—become opportunities for learning about patient care delivery processes and for improving those processes.

The Mount Sinai review process is an example of collaboration between line managers and experts in organizational research. Acting alone, a manager might design a survey lacking in scientific integrity with a high risk for producing biased data. Without active managerial participation, a researcher might well produce an elegant questionnaire that lacks relevance and flexibility. The fact that the review process has continued to function and continuously improve for almost a decade is testimony to the usefulness of this approach.

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Book Reviews

Quality Improvement

A Review of Five Books and a Personal Overview

Charlotte Muller, Ph.D.

Guidelines for Clinical Practice: From Development to Use. Marilyn J. Field and Kathleen N. Lohr, editors. Washington, DC: National Academy Press, 1992. 440 pp, index, pb, $34.95. ISBN 0-309-04589-4

Assessing Quality of Health Care: Perspectives for Clinicians. Richard P. Wenzel, editor. Baltimore: Williams & Wilkins, 1992. 560 pp, $78.00. ISBN 0-683-089242

Measures of Need and Outcome for Primary Health Care. David Wilkin, Lesley Hallam, and Marie-Anne Doggett. Oxford: Oxford University Press, 1992. 320 pp, $65.00. ISBN 0192618180 (out of print)

Who Survives Cancer? Howard P. Greenwald. Berkeley: University of California Press, 1992. 304 pp, $25.00. ISBN 0520-077253

Managing Quality: A Guide to Monitoring and Evaluating Nursing Services. Jacqueline Katz and Eleanor Green. St. Louis: Mosby-Yearbook, Inc., 1992. 272 pp, $37.95. ISBN 02620-080162620X

THE VALUE of specific medical care services to health has many ramifications for decisions affecting individual lives and the social structures connected with health care. It enters into the design of insurance benefits (what services ought to be covered?) and into codes of professional and institutional conduct, which are in turn recognized by courts adjudicating malpractice suits and by malpractice insurance companies. The effects of services on health are central to medical societies' programs for self-discipline and member education, and to the education of consumers to develop informed choice and informed consent. Judgments about services are also essential for assessing equity of access to "quality" services.

From an economic perspective, systems of quality maintenance and improvement seem to have become a competitive necessity for provider organizations operating in a market. In public sector economics, quality issues are tied to both immediate and ultimate care costs, as well as to indirect costs associated with ill health, and to the reasonableness and fairness of any proposed rationing of health care. Economically speaking, achieving quality in specific aspects of care (such as surgery or the rational prescribing and error-free administration of medications), like any other objective, involves resource costs. For that reason, selection of the means to achieve quality and the assignment of priority are significant areas of decision today. For example, based on gains to quality compared with cost of execution, what should be the respective places of retrospective reviews, concurrent monitoring, and precertification?

Five books that shed light on some feature of the complex enterprise of moving the U.S. health care system toward quality goals are the subject of the present review. *Guidelines for Clinical Practice,* edited by Marilyn J. Field and Kathleen N. Lohr, deals with a major national investment in the development of practice guidelines supported by scientific evidence. *Assessing Quality of Health Care: Perspectives for Clinicians,* edited by Richard P. Wenzel, deals with improving the ability of medical clinicians and others in hospitals to implement the current quality improvement agenda sponsored by the Joint Commission on Accreditation of Healthcare Organizations. *Measures of Need and Outcome for Primary Health Care,* by David Wilkin, Lesley Hallam, and Marie-Anne Doggett, reviewing alternative measures of need and outcome applicable to primary care, signals by its very existence that ambulatory care will be an increasingly vital arena for evaluation of performance.

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Who Survives Cancer? by Howard P. Greenwald, which explores factors that contribute to chances of surviving cancer, is a reminder that the proof of the pudding is in the eating and is a corrective to preoccupation with intermediate goals that may be unproductive. Finally, a book on organizing quality improvement structures and processes in hospital nursing departments, *Managing Quality: A Guide to Monitoring and Evaluating Nursing Services,* by Jacqueline Katz and Eleanor Green, takes us mentally to where much of the action is. Even the neatest algorithm for clinical decision making depends on assumptions that hospital services will be characterized by timely and accurate performance of a myriad of steps and by caring attitudes toward patients.

Guidelines for Clinical Practice. The Field-Lohr book represents the work of an expert group, the Committee on Clinical Practice Guidelines of the Institute of Medicine, that has promoted science-based guidelines to improve and measure quality of clinical care and to clear the system of the costs of inappropriate care. Such guidelines are intended to be the basis of medical review criteria, and are needed now because the proliferation of efforts by specialty societies and others to provide formal guidance for clinical decisions is marked by a degree of chaos in selecting topics to focus on and in procedures for identifying guideline elements and attaining consensus. The American Medical Association is said to have listed 1319 "parameters"; the U.S. General Accounting Office has commented that no two specialty societies "have produced similar guidelines for similar reasons in a similar fashion."

Some of the desirable attributes of guidelines relate to the validity, flexibility, and so forth of the contents; others relate to skill in developing them and persuading physicians and organizations to adopt them. Medical review criteria, used to determine if guidelines have been followed in giving care, have somewhat different attributes because they must demonstrate sensitivity and specificity, discriminating between the bad and the good in actual care, while not being burdensome to apply.

Guidelines need to be updated at scheduled times, and thus have a limited life expectancy; furthermore, the cost of development is known to be extremely variable across conditions, procedures, and specialties. Literature reviews alone have cost as much as $235,000. Because some, perhaps a substantial part, of this outlay must later be repeated, given the changing world of science and of client rights, a considerable investment may be involved. Yet the net effect of guidelines on costs cannot be predicted. The Committee on Clinical Practice Guidelines has warned against overoptimism in this respect, while declining to include cost effectiveness as a factor in formulating guidelines. Cost effectiveness would be partially introduced, in an indirect way, if future priorities for practice guidelines emphasize services that are probably overused today, implying that indications could be narrowed without loss to health, but the committee notes that underuse is also a problem in achieving quality.

The evaluation of guidelines and their implementation, through educational efforts directed at physicians, for example, emerges as a current social task. If, as is stated in this book, physicians are alienated by quality assurance programs that emphasize individual malfeasance, gaps in data collection may affect the assessment of actual performance, and organizations may confine themselves to reporting variation around a mean rather than identifying departures from "good" care.

The book presents an excellent history of the interest of governmental and nongovernmental organizations in adapting quality assurance to current needs and production processes in health care. The introduction of continuous quality improvement (CQI) into hospitals has been based on extending to hospitals the work of Edward Deming and others. CQI rests on a set of reinforcing principles for achieving quality nonpunitively; the emphasis is on system defects, use of statistical methods in planning and control, reliance on self-monitoring and learning from mistakes, the standardization of processes, and establishing a linkage between processes and outcomes. Feedback to the practitioners or other actors in health care supplies the channel for "continuous" improvement. Algorithms fit into this because they depend for success on correctness in process details. But as practiced so far, CQI has tended to rely on implicit judgments and local statistics and to focus on nonclinical aspects of service. Consultants have developed a thriving industry.

Sixteen examples of clinical guidelines are appended, carefully chosen to represent different clinical orientations (a technology, a condition), and purposes (screening, part or all of a treatment), complexity of content, format (text, tables, if-then statements), and intended users. The variation in these samples is amazing. Some of the diagrams excel in clarity—for instance, the use of different box shapes to represent clinical states in the course of care, a question, or an action to be taken. But the driving logic could be compromised by flaws in process, such as delays in getting laboratory results or variation in interpreting a history. A guideline for tracking metabolic acidosis, shown in computer language, seems to require a great deal of translation or special training for accessibility, which could inhibit detection of flaws in logic.

Another problem of the current pluralism in guideline creation is that one patient or group of patients can be subsumed under several different types of guidelines arranged on different axes, for example preoperative care, a major condition, and intensive care nursing. Could they conflict, or duplicate effort, in implementation? Possibly hospital-wide coordination could settle this.

Finally, guidelines stated in an expository text seem to provide considerable leeway for variation in decision making.

Guidelines for Clinical Practice is an indispensable resource for basic understanding of quality improvement as a medical and governmental activity today. If those groups that are motivated to take responsibility are also committed to what they regard as equilibrium—retaining control of their specialty, avoiding standard setting by government, diminishing the role of other parties—there will be limits on what can be achieved. For example, once the elements of meticulous performance of surgery are specified, including indications, actual performance may be compared with this set of rules, even when it is not clear that survival is better than under alternative nonsurgical treatments.

Assessing Quality of Health Care: Perspectives for Clinicians. In hospitals, which have been the prime venue for quality assurance activities in health care, epidemiologic methods are used increasingly to explore and improve quality. The formation of a productive alliance between a hospital's administrators and its physicians is essential to meet the current demands of outside organizations for evidence that care is of acceptable quality. This is the focal argument of the book edited by Richard P. Wenzel, faculty member and hospital epidemiologist at the University of Iowa Hospitals and Clinics.

In 28 chapters, 15 by single authors and 13 by teams, a guide to playing the necessary roles in such a productive alliance is offered. The section entitled, rather vaguely, "Organizing for Change" starts with an overview by Donabedian of his influential analytic framework for understanding and measuring health care quality. Then several methodological chapters give a useful introduction to decision analysis, meta-analysis, how to evaluate clinical studies, and standard setting. The centerpiece of this methodological section is a thorough presentation and critique of major alternative measures of severity of illness; some such measure is essential in adjusting outcome data so that results are not wrongly attributed to an intervention when the patient's prior condition was largely responsible. Severity measures also show longitudinal change in a patient's state of health and become a direct measure of outcome. This material should be illuminating to medical and nonmedical professionals involved in hospital quality activities; a good review and update are provided, especially in the chapter on measuring severity, even for those familiar with statistical reasoning.

A presentation of the key requirements of quality assurance and the concept of continuous quality improvement introduces readers to the task of organizing a hospital-wide surveillance program. This is complemented by a sequence of chapters detailing quality assurance mechanisms and experience in various medical specialty departments and other hospital subentities, such as clinical and microbiological laboratories, the pharmacy, and the critical care unit. (Editing could have avoided multiple repetitions of listings and explanations of the JCAHO's ten-step process of quality assurance.)

Each department has its own specific implementation problems. Thus, the low rate of untoward events now occurring in anesthesia is said to limit the usefulness of statistical analysis of outcomes to identify poor work, resulting in reliance on documented processes for evaluating care. At the University of Iowa Hospital, residents and staff fear that the purpose of data collection is "to chastise and humiliate guilty individuals." This is a disincentive to providing documentation. In pediatrics the applicable standards depend on the scope of services offered; for adequate pediatric care in a tertiary care facility, standards for diagnostic radiology, surgery, and other services must be met, in addition to standards for decision making by pediatricians. This illustrates the need for hospital-wide coordination of quality improvement efforts rather than departmental self-governance.

The format as well as the language of the book indicate membership in a world in which the main actors are the physicians and the hospital administrator, moving within an environment of regulation (chiefly accreditation and its implications for reimbursement), competition, and legal decisions governing ethical conduct. Consumer satisfaction with care and the interpersonal process that consumers of medical care experience is considered a valuable aspect of quality in Donabedian's work, and consumers' perspectives entered the regulatory framework with recognition of the rights of residents in long-term care facilities through the Omnibus Budget Reconciliation Act of 1987 and its amendments in later years. But in the world assumed in this book, consumers mainly rely on enlightened providers and societal standards expressed through regulation. Although consumers are generally expected to maximize their utility by choosing between supply sources, medical consumers are not always able to shift their custom to other facilities, and they are not regularly a part of standard setting.

Measures of Need and Outcome for Primary Health Care. Quality of care outside the hospital is bound to be a significant component of a reformed U.S. health care system, because universal access is a satisfying goal only if flaws in the care received do not deprive recipients of the social minimum of attainable health. The book by Wilkin and others comes from a center for primary care research in Manchester, England. It makes an important contribution to the study and evaluation of primary care by exploring the measurement of needs and outcomes—opposite sides of a coin, since "an instrument which measures pain can be used to assess the need for pain relief and the outcome of administering an analgesic." The prevalence of chronic diseases has tended to shift attention to measures evaluating factors other than cure and survival, although the authors state that the content of such measures has changed less than one might suppose. The consequence of disease for individuals, families, systems, and society is one such appropriate concept. Satisfaction is also a proper object of concern, but is elusive because of its relation to expectations. Additionally, the aspects of care to be evaluated in terms of satisfaction should be specified; studies have indicated that provider conduct, accessibility, and continuity account for much of the observed variance in satisfaction.

The main body of the book is a systematic analysis of 40 measures either developed for primary care or potentially applicable there, grouped as measures of functioning, mental illness and mental health, and social support; multidimensional measures such as the Sickness Impact Profile; disease-specific measures; measures of patient satisfaction; and miscellaneous measures, of pain management, for example. The discussion of each measure encompasses its purpose, background, and evolution; a description; methods of scoring and administration; acceptability to patients; reliability and validity; population and service settings; comments; and references. Included are older measures that were pioneering but have been superseded by new measures to which they contributed. The tone is forthright but judicious, and specific situations in which a measure may be valuable despite its limitations for other uses are pointed out. Applicability of a measure to older patients is noted throughout. This book can be used as a reference to look up a measure that may have been recommended for a particular evaluation purpose, but reading it all is valuable. The likely effect is to raise one's level of understanding and critical judgment. Missing, perhaps simply unavailable, is information on the cost of using different measures.

The overall appraisal of the field by the authors is that creators of measures often have produced skimpy documentation, that evidence of reliability and validity is often limited to particular categories of patients and settings, and that, regrettably, the ability of measures to detect changes such as treatment effects is not usually evaluated. All the measures of satisfaction reviewed suffer from weaknesses. In other subject areas, such as physical function, the authors believe existing measures to be generally adequate, making the development of new measures wasteful.

In applying the thoughts in this British book to the United States we should think about our own recent past and future. Revival of infectious diseases through alterations in immune systems may change the nature of instruments required in evaluating ambulatory care. On the organizational side, the shifting of certain kinds of inpatient care to outpatient sites, and the use of outpatient sites for postdischarge followup, might interest those whose attention has centered on inpatient services to increase investment in evaluating ambulatory care. More generally, ambulatory care will be a crucial component of health care redesign in the United States as national coverage within budget constraints evolves. We need to have patient-specific measures that will promote rational triage, and we need to prepare to measure efficiently the health consequences of care under different conditions of practitioner type, access rules, financial coverage, continuity, and so forth.

Who Survives Cancer? Examination of survival from cancer by a social scientist integrating medical, epidemiological, and psychological data provides a different perspective on quality issues. Howard Greenwald began his research on cancer in connection with a project to study pain among cancer patients in the Seattle area, later investigating their ability to continue working, and, finally, determinants of survival. The product of this latest effort is the Seattle Longitudinal Assessment of Cancer Survival. Reviewing the body of evidence from this study, the book evaluates the implications for survival of patient characteristics, organizational forms of health care delivery, participation in experimental protocols, and emotional factors. The value of prevention and early detection is discussed.

What connection does this book have with quality of care? It analyzes pathways—including rates of detection, choice of treatment, type of hospital—by which economic resources, class, and race may influence chances of survival of different forms and sites of cancer. It examines the influence of emotional factors on survival (Greenwald finds that the evidence for influence is mixed). Thus the book provides a background for considering patient-centered aspects of quality improvements when forming goals and priorities. That could mean that in the exploration of patients' attitude, mood, and satisfaction as a step toward improving care, health care managers and providers should aim for improvements that have meaning for patients whose prognoses are currently limited by the state of medical knowledge, but should also strive to strengthen the pathways that could maximize survival.

In comparing HMOs with fee-for-service care, Greenwald concludes that low-income patients, but not others, had better survival in HMOs, but not because of rapid detection or more intensive services. It is possible that those low-income patients who were more motivated to take care of their health joined HMOs and were enabled to do so, and that they got better care for conditions accompanying their cancer. However, competition could lead HMOs to reduce their commitment to preventive services.

From the perspective of improving survival, the distinction between types of cancer is critical. The author points out that some types are more responsive to early detection than others (currently, lung cancer is not), and that some forms are highly resistant to treatment. On prostate cancer, for example, the author says: "Physicians have not reached agreement on appropriate treatment. . . . Uncertainty arises in part from the highly variable nature of the disease. . . . Physicians cannot always ascertain the 'malignant potential' of localized prostate cancer through microscopic examination." Some advocate extensive surgery plus radiation for early-stage disease, others eschew aggressive treatment to avoid side effects incurred without expected prolongation of life. Thus the consensus needed to form guidelines on prostate cancer, as on some other forms of cancer, is elusive.

Other evidence indicates that good results depend on prompt referral for treatment after diagnosis, as well as prompt movement from screening to definitive diagnosis; delay or inaction at some screening centers precludes realizing the gains of early detection. Patients with weaker previous relations with the health care system were the most likely to be the ones affected, but an alienating automated screening process seemed to contribute to their failure to act. Here is meat for quality improvement in both the conduct of screening and the coordination of stages of care.

Greenwald's work disaggregates a somewhat idealized cancer control process that is often pictured, and locates weak points. It helps identify areas in which guidelines are achievable and desirable, and suggests the need for guidelines, evaluative plans, and regulatory provisions that would bring public and private hospitals closer to parity. If the payment system were shored up to prevent barriers to important forms of care, the payoff from guideline development and implementation, affecting the sequence of services received by those who do connect with potentially appropriate care, should be enhanced.

Managing Quality: A Guide to Monitoring and Evaluating Nursing Services. The last book reviewed here brings us back to the hospital setting and to the adaptation of nursing management to the current responsibilities of institutions for delivering quality care cost effectively in the context of prospective payment methods of reimbursement. This book professes to provide a step-by-step plan to translate the agenda of and the process recommended by the Joint Commission on Accreditation of Healthcare Organizations into a quality assessment program for nursing. The program focuses on high-risk, high-volume, problem-prone, and high-cost aspects of nursing service. Nursing is redefined as a service business, with clinical, professional, and administrative aspects, following Deming's conception of quality improvement as a major business strategy. Satisfactory performance is necessary to retain accreditation and access to payment from third-party systems and to thrive in a competitive market for hospital care.

The business orientation is present in the circumstances of the book itself, for the framework for quality management offered, called THE BLUEPRINT, is a proprietary product being marketed by the authors, operating as consultants. They state that it has been used successfully in hospitals in the United States and Canada, but do not present details.

A key concept is that when a problem is discovered, the response is to ask whether it arises in the clinical (patient-related), professional (team-related), or administrative (system-related) domain. Another central concept is that continuous quality improvement requires practice guidelines for nursing departments. The emphasis should be not on checking off whether various tasks have been performed or on collecting volume data but on whether the guidelines have been followed. Evaluation is explicitly added to Donabedian's well-known triad of dimensions of quality—structure, process, and outcome.

The book has the commendable objective of preparing hospital nursing departments for a more vigorous role in assuring quality. It contains examples of indicators being developed under the sponsorship of the JCAHO relating to anesthesia, oncology, and other services. It gives examples of a variety of forms for organizing necessary data, such as tracking pressure ulcers by month and determining whether the number is above the threshold for investigation. It shows exactly how to derive the standard deviation for the medication error rate, thus creating such a threshold. It exhorts, explains, and works at raising the confidence level of nurses.

The work does, however, exhibit haste and uncertainty of focus on what level of background and experience readers are expected to have. The material on indicators wavers between defining them as rates—occurrences over a relevant denominator—or as numerators alone, and in one instance presents the wrong denominator. The distinction between "high-risk" and "problem-prone" activities is not quite clear when the administration of medications with serious side effects is classed as in the latter group. The information on measuring performance with respect to the medication error rate, while clear, does not mention relating the number of errors to the patient census in a given month or distinguishing between serious and less serious errors. At what level of responsibility will these distinctions be made? Finally, it is hard to accept the authors' confidence that the quality assurance professional "can create an atmosphere of nonpunitive, safe data reporting." Are nurses sure of their safety when other writers note that physicians in training and in practice are not free from fear of consequences? More depth is needed to convert a book that is selling a concept into a true step-by-step guide.

Discussion

Today the quality movement is embedded in and burdened with the various attributes of the current health care system, notably lack of agreement on social objectives, conflicts of interest, and fragmentation of responsibility. Yet the improvement of the whole system depends in part on solving problems of quality. Difficult as this task is, self-awareness is surely a necessary part of moving forward. This sampling of current writings on health care quality definition, measurement, and achievement suggests that the proliferation of efforts is more visible than their yield, and that one cannot be confident that continuing current approaches will produce incremental improvement. Readers are invited to examine these and other publications and judge for themselves.

Professional groups, institutional providers, and sellers of monitoring and evaluation services have established themselves, each in their own way, as guardians of quality. In addition, agencies of government have selected particular regulatory objectives centering on reimbursement from public programs (the Health Care Financing Administration) or legitimizing access to private markets (the Food and Drug Administration). Actually, the public and the private spheres overlap in that copayment by Medicare enrollees involves the providers with personal spending, while drug manufacturers' markets include governmental health care facilities. Insurance companies protect their own finances by their rulings on medical necessity in the design of benefits and the processing of individual claims.

The different parties involved in monitoring quality have their own objectives and constraints in creating or applying guidelines, standards, and methods of review, and in determining consequences of practitioner or facility performance. The product of these activities is subject to inconsistencies and gaps such that neither a desired and definable quality level nor a path of continuous improvement is assured. Suspicion, sometimes justified, that costs may be a more prominent concern to various regulatory bodies than quality of care, and the existence of benefit restrictions that create difficulties for clients strengthen the private motivations of those delivering care for active and passive resistance to challenges to previous autonomy in clinical decision-making, such as making sure the record shows the requisite indications for a set of services. The necessary reliance for documentation on those whose livelihood may be threatened by statistical or textual evidence of deficiencies tends to disable the self-regulatory efforts of provider organizations, including efforts at defining good care.

Cost effectiveness is a hot potato. Its omission from guidelines is deceptive, because assumptions about the direct and indirect economic effects of clinical decisions, choice of medical procedures for consensus development, and task allocation in hospitals are to be found everywhere. They are embodied, for example, in physicians' judgments about continuing intensive care in specific cases. Yet personal or institutional habits are not an adequate way of paying homage to resource scarcity, first, because precise analysis may yield better use of resources (determining the most cost-effective interval for cervical cancer screening), and second, because it is not acceptable to rely on the provider of services as the perfect agent for expressing the value preferences of patients and families or other members of society who may be affected.

The intention to ground quality efforts on scientific methods is unimpeachable, yet medical research and the publication of its results are not free from problems. The conduct of clinical trials has greatly benefitted by the progress of epidemiology, but clinicians have sometimes been reluctant to enroll patients when a treatment protocol already in use has been shown to be effective; moreover, results of trials conducted under highly controlled conditions may not be perfectly applicable to more heterogenous populations and circumstances. Meta-analysis was intended to enhance our ability to distill knowledge from disparate research studies, but it too has varied in validity, as currently practiced. The association of enrollment in trials with access to services greatly longed for by the seriously ill has complicated the research enterprise. Previous exclusions based on age and gender, whether prompted by needs of investigators for sufficient sample sizes and other features affecting publishability, or expressive of bias, have affected the utility of results as a guide to practice. While we apply ourselves, as we should, to implementing the science that we possess, no piece of the quality movement should be above scrutiny. Furthermore, the entire process should be examined in terms of its cohesion and resistance to being derailed by historical boundaries between groups and organizations, either the different specialties and hospitals or consensus-forming bodies, practitioners, and payers.

Grand Rounds

Controversies on Screening for Cancer of the Prostate

Martin I. Resnick, M.D.

In this discussion of carcinoma of the prostate I want to emphasize the controversies related to screening and methods of screening, first by reviewing the controversies related to screening in general and whether we should screen, then by reviewing some of the screening methods, such as digital rectal examination, ultrasound, and prostate-specific antigen (PSA). This overview does not necessarily answer all questions, but at least makes the issues clear.

Many of those issues were aired in 1992 in three articles (1–3) and an editorial (4) in a single issue of the Journal of the American Medical Association, and in subsequent letters to the editor (5–10) questioning screening for cancer of the prostate, particularly PSA. One of the articles, by Johansson et al. (1), presented data which addressed the issue of observation in lieu of treatment for cancer of the prostate; another, by Carter et al. (2) of Johns Hopkins, reported that the rate of change in PSA over time improved the detection of cancer of the prostate; the third article, by Crawford et al. (3), was on the effect of digital rectal examination on PSA levels, and the editorial by Oesterling (4) dealt with improving PSA screening. The letters were interesting, and raised many of the relevant questions I discuss here.

Does Screening Reduce Mortality?

The purpose of screening is not necessarily to diagnose more disease, although screening obviously does accomplish that; the purpose of screening is to reduce the mortality from the particular disease. For instance, studies utilizing spectrum cytology and routine chest x-ray as a means of detecting early carcinoma of the lung in a specific patient population have compared screened patients, or study patients, with an unscreened general population. The results indicated an increase in the detection of cancer of the lung in the screened population. However, when these patients were followed up after treatment, the mortality in the screened and the unscreened groups was no different. Because the screening tests had no impact on mortality, it was concluded that screening for cancer of the lung using spectrum cytology and chest x-ray was not beneficial. In contrast, many studies utilizing mammography to screen for cancer of the breast have demonstrated that in women over 50 years of age who have a yearly mammogram, mortality from cancer of the breast is reduced by about 30%. The role of mammography in women younger than 50 remains controversial because mortality has not been shown to be reduced with use of yearly mammography.

For cancer of the prostate we do not have any information on the impact on mortality of routine screening by any method. I do not think there is any question that we will detect more cancer of the prostate. We are certainly seeing that now. But whether the routine testing will have any impact on mortality has been an area of much concern.

There are two ways to reduce mortality from cancer of the prostate: to decrease the incidence of disease, or to improve therapy. Decreasing incidence is not likely to occur because the incidence of prostate cancer seems to be increasing. Note how the incidence of cancer of the lung, in the United States has over the past 20 years declined among men and increased among women. It has been estimated that in several years mortality

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Adapted from the author's Grand Rounds presentation at The Mount Sinai Medical Center on December 10, 1992. Final revision received April 21, 1993. From the Department of Urology, Case Western Reserve University School of Medicine, Cleveland, Ohio. Address reprint requests to Dr. Resnick, the Lester Persky Professor of Urology, Chairman, Department of Urology, University Hospitals of Cleveland, 2074 Abington Road, Cleveland, OH 44106.

due to cancer of the lung will decrease among men, whereas today more women in the United States are dying of cancer of the lung than of cancer of the breast. These changes in incidence and in mortality have occurred primarily, because over the last two decades smoking among women has risen whereas among men smoking has decreased.

Another means of reducing mortality is to improve therapy. Unfortunately, therapy has had no significant impact on mortality for localized carcinoma of the prostate for at least two decades. Improvements have been achieved in therapy of testicular malignancies, particularly with cisplatinum-based chemotherapy, but I see nothing on the horizon that will have any impact on the mortality rate of cancer of the prostate. A great need is to try to find a way to alleviate or cure metastatic cancer of the prostate; that, would certainly lessen the need to detect the disease early.

But today the only way to have an impact on mortality from cancer of the prostate is early detection, and it is for this reason that early detection has received attention. However, I must point out that there are no data to indicate that early detection can indeed reduce mortality.

Treatment or Observation?

The other controversy about cancer of the prostate centers on whether we have to treat patients with localized cancer of the prostate. Several studies have followed up for ten years patients who have localized disease (8). In these studies most of the patients went on to develop progressive disease and approximately 25% went on to develop metastatic disease. But death due to prostate cancer, even though patients would have required intervention, usually by endocrine therapy, is relatively low. Only 8% of the patients died of prostate cancer during that ten year follow-up (12).

The majority of patients with low-grade tumors who were followed up for a ten-year period died of other causes. Patients with high-grade disease had a higher death rate from cancer of the prostate. These studies have been criticized because they are heavily weighted toward patients with low-grade disease, but I feel that only the minority of patients with low grade disease who are not treated go on to develop metastatic disease, and the death rate from prostatic cancer is significantly less than the death rate from other causes. Though the argument can be made that these studies are heavily weighted toward an older population, the point is that a 70-year-old man with a grade 1 or 2 malignancy is less likely to die of untreated prostate cancer than from other causes.

Cancer of the prostate has a high prevalence in our population—30% in men over 50 and at least 60% to 70% in men over 70. The chance of dying of prostate cancer is 2%. The question often raised is, Do we want to identify and subsequently treat all patients who have cancer of the prostate when a relatively low percentage of patients require treatment? These are more philosophical arguments, but I think they are real and require consideration.

In the United States there are roughly 24 million men over age 50; assuming a prevalence of the disease of 30%, a little over 7 million men have the disease. In 1992, cancer of the prostate was diagnosed in 132,000 men, and there were 34,000 deaths. Whether the measures we are taking today will have any impact on this mortality figure remains unknown, for the reasons I have mentioned.

Methods of Screening

What would be an ideal screening test if we wanted to screen? We want a test with high sensitivity and specificity, and also with high positive and negative predictive value. The test should detect localized disease with little or no risk and morbidity. The test should be inexpensive and rapid. The widespread use of the test should reduce mortality by differentiating patients who have clinically significant disease which would respond to treatment from patients who have what can be referred to as latent cancer of the prostate, or cancer of the prostate that is not placing them at risk.

The limitations inherent in the current situation are obvious. Prostate cancer is a disease with a high prevalence rate and a relatively low incidence of clinically significant disease. Most important, no current screening tests are able to identify and differentiate those individuals with biologically aggressive disease from those individuals who have disease that tends to be more dormant.

Ethical arguments have been raised about screening. One ethical argument centers on this question: given limited resources in this country, should we as a society put several billions of dollars into the treatment of patients with cancer of the prostate? I believe the question of resources is going to become an increasingly important issue.

Another ethical question has to do with unnecessary treatment. If a group of men who are not at risk of either dying of or sustaining any morbidity from the disease are diagnosed and treated, one can only assume that some will not benefit from the treatment, some will in fact have significant morbidity from the treatment, and some will die of the treatment. This line of thinking has been used to argue the value in general of screening populations, and the value in particular of screening populations for cancer of the prostate.

Sensitivity, Specificity, Predictive Values. Sensitivity is the ability of a test to detect a disease. How good a test is it? Mathematically sensitivity is the ratio of the number of patients with true disease (the number of true positive) and the sum of those who had positive tests and those who had false negative tests.

Specificity is a measure of the ability of a test to exclude disease. It is the number of patients who have a true negative study divided by the total number of individuals tested who did not have the disease, that is, the sum of those who tested negative and those who had false positive results. A test should reveal who indeed does have the disease, and who does not.

The positive and negative predictive values are useful in respect to the prevalence of the disease in the population. The positive predictive value is the ratio of the number of true positive studies to the sum of the numbers of both the true positive and false positive studies. A test that yields no false positive studies has 100% positive predictive value, which means that everyone who tests positive will have the disease, an obviously good but unattainable outcome.

The negative predictive value is the ratio of the number of individuals who have true negative studies to the sum of the number of patients who have true negative and false negative studies. That value is ideally 100%; at 100%, no one who tests negative has the disease. Unfortunately, most tests are not good for diagnosing the disease, or for excluding it in the general population.

A major problem with many of the reported studies is the nature of the population being evaluated. We often discuss screening and early detection in the general population, but who is being tested? Most of the reports give results from a selectively referred, or symptomatic, population; many of these patients are specifically sent for evaluation for cancer of the prostate because they have various symptoms, including voiding difficulties and pain. A population solicited by placing an ad in the newspaper, or in a hospital journal will generate a group of subjects very different from those drawn at random. The ability of the test to detect cancer of the prostate will be highly dependent on the population being studied.

Length-Time Bias, Lead-Time Bias, Overdetection. Some other concepts related to screening and terms which I think are important are length-time bias, lead-time bias, and overdetection.

Length-time bias refers to bias introduced by the length of time the disease has existed in a patient or a group of patients. A symptomatic population will usually have larger and more aggressive tumors than those detected in an asymptomatic population. Asymptomatic tumors usually occur at a lower stage of the disease and entail a longer natural history of disease than symptomatic tumors. Patients who have symptoms often have more advanced disease which progresses more rapidly. When outcomes in a symptomatic population are compared with those in the general population being screened, the general population always does better.

Lead-time bias refers to the bias that may arise due to the interval between diagnosis and death. Often the time of diagnosis is related to when the symptoms develop. For argument's sake, say that period is 10 years after a patient contracts the disease. If a test is developed and the tested subjects, representative of the general population, live another five years (that is, the lead-time bias is 5 years), one might conclude that there is a 5-year benefit to those who were tested. However, in reality all we may be doing is identifying the disease earlier, rather than having an impact on the natural history of the disease. That is the lead-time bias.

Overdetection I have already alluded to. We will be detecting with increasing frequency more and more men who have cancer of the prostate but are not at risk of dying from it. Once diagnosed, they will probably be treated. The morbidity and mortality entailed by treatment in an asymptomatic population may be shown to surpass the morbidity and mortality of untreated disease.

Screening Tests

Digital Rectal Exam. In a variety of studies (13–15) assessing the sensitivity/predictive value of digital rectal exam, the detection of a palpable nodule ranges from 1.2% to 1.6%. Of this group, roughly 25% will be found to have cancer of the prostate.

Routine screening by digital rectal exams increases the proportion of patients who have cancer of the prostate confined to the prostate (Stage B carcinoma) and decreases the detection rate of metastatic disease compared to the unscreened population. What is interesting is that the mortality rate from cancer of the prostate in the two populations is not very different. Many patients with seemingly clinically localized disease will have more extensive disease when they are fully evaluated. In summary, while screening by digital rectal examination may increase survival, there are no data yet to indicate that screening by digital rectal examination impacts on mortality (16).

Prostate-Specific Antigen (PSA). Many men who have an elevated PSA level will not have cancer of the prostate because they will have benign hyperplasia. As a group, men with nonmetastatic, or localized, cancer of the prostate will have higher PSA levels than patients without cancer of the prostate. However, a number of men who have localized cancer of the prostate will have PSA levels within the normal range.

PSA poses the same problems as digital rectal examination. Roughly three quarters of patients who had no evidence of cancer of the prostate have PSA levels within the normal range. However, roughly a quarter of the population will have elevated levels, most being in the 4–10 μg/L range, but there are patients without cancer of the prostate whose PSA levels are greater than 10. Unquestionably the false positive rate is significant as a result of the test and the presence of benign hyperplasia in the population.

Experience also has indicated that PSA does not detect everybody with cancer of the prostate. Indeed, slightly over 40% of men with organ-confined prostate cancer have PSA levels in the normal range. Therefore the problems with PSA are the same as the problems with digital rectal examination: a high false positive rate and a significant false negative rate. Almost half of the patients with theoretically curable disease, the group we most want to identify, have false negative results, that is, their PSA levels are within the normal range.

Experience indicates that of patients with clinically localized disease and PSA levels ranging from 4.1–9.99 μg/L, just over half have pathologically localized disease. Most of the patients whose PSA levels exceed 10 μg/L have more advanced disease at the time of their radical prostatectomy. So that is the other problem with PSA levels—a level of 10 μg/L is not going to be sensitive enough to detect patients with localized disease. PSA, for the reasons I have discussed, is an imperfect test.

In summary, about 25% of patients with benign disease have PSA values greater than 4 μg/L and another 4%–19% have values greater than 10 μg/L. On the other hand, roughly a third of patients with organ confined prostate cancer will have false negative PSA levels of less than 4 μg/L and if the cut-off value is raised to 10, the false negative rate goes up to roughly two thirds. Whether a rate of change in PSA levels exceeding 0.75 μg/L per year will prove to be of diagnostic value as proposed by Carter et al. requires further study (9).

Ultrasound. The problems of ultrasound testing with false positives and false negatives are the same as with the other tests. The positive predictive value indicates that if a peripheral zone hypoechoic area is observed on ultrasound, the chance of having cancer of the prostate is roughly 20%–25%. A significant number of patients who have cancer of the prostate will not have any ultrasound abnormalities, resulting in many false negative studies. This was demonstrated nicely in a study of patients with localized cancer of the prostate confined to one lobe (17). Prior to radical prostatectomy, transrectal ultrasound examination was performed and a whole-mount preparation of the removed specimen was examined. Of the 59 patients studied, 25 had contralateral malignancies that were not detected by digital rectal examination. Ultrasound predicted cancer of the prostate in only 13 (52%) of those patients, thus missing the diagnosis in 48% of the patients. Unfortunately, this is a significant false negative rate. Of the patients who did not have any contralateral malignancy, a false positive study was present in one third. Therefore, ultrasound used alone is not reliable for detecting or excluding the presence of cancer of the prostate. Other studies have reported comparable data.

Another interesting point about ultrasound is that a positive study (showing abnormal results) is more likely to be reported when the diagnosis of cancer requiring biopsy is suspected. In my own mind, the more biopsies performed, the more cancer of the prostate is going to be found. We are detecting more cancer of the prostate with increasing frequency of biopsy because we are dealing with a disease that has a prevalence rate of 30%.

Combination Studies. Cooner et al. (18) found a detection rate of cancer of the prostate of 15% in their series of men. Digital rectal examination, PSA, and transrectal ultrasound were evaluated. The report indicates that the combination of diagnostic studies has a greater predictive value than any single evaluative study used alone. If all tests are positive, a patient has a high probability of having cancer, and if all studies are negative the probability of cancer is less likely.

Future Answers?

The National Institutes of Health has committed something like $72–75 million to study cancer of the prostate, cancer of the lung, cancer of the colon, and cancer of the ovary. Fifty thousand patients will be screened and compared to a nonscreened, or control, population. All patients will have three annual chest x-rays and sigmoidoscopies, and participating men will have digital rectal examinations and tests for PSA levels. Participants with abnormal results will have subsequent evaluation, and treatment will be instituted. Patients will be followed up for ten years looking at mortality. It is hoped that the following questions will be answered: Should we screen? Does screening have an impact on mortality for any of these diseases? If we are going to screen, what is the best way? Are these the best tests? Is the sequence the best? Nobody knows. Unfortunately I do not have any answers.

I hope that I have given you a little more insight into this problem and that with more insight you will be better able to advise your patients appropriately.

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Abstracts

The abstracts presented here, all by principal investigators in the Department of Medicine of the Mount Sinai School of Medicine (which includes the affiliates Beth Israel Medical Center, the Bronx Veterans Administration Medical Center, and Elmhurst Hospital Center), in New York City, were exhibited as posters in the Department of Medicine Eleventh Annual Research Day, October 5, 1993. Abstracts 16, 21, 22, 38, 39, 41, and 42 are omitted here because they have been published elsewhere.

Ten abstracts by students, fellows, and house staff working in the Department of Medicine received Eleventh Annual Department of Medicine Research Awards and were presented orally at a Special Grand Rounds the same day; these are identified by asterisks (*).

Research Day in Medicine 1993

Cardiology

1. **Are Moderately and Severely Hypertensive Women Misclassified and Overtreated?** Joseph A. Diamond, MD, Maria Ardeljan, RN, Arlene Travis, RN, Kevin Martin, MD, Craig Wilkenfeld, MD, Lawrence R. Krakoff, MD, Robert A. Phillips, MD PhD. Hypertension Section, Division of Cardiology, Mount Sinai School of Medicine, New York, NY.

Criteria for diagnosing and treating moderate and severe hypertension has been derived from studies that often excluded women. It has been shown that gender may influence both the natural history of hypertension, and the effects of antihypertensive therapy on treatment outcome. In mild hypertension, a "white coat" response is more prevalent in women. The goal of this study was to determine if ambulatory blood pressure monitoring may lead to more accurate classification of hypertension and of cardiovascular disease risk.

We studied 25 asymptomatic and untreated patients (11 men and 14 women) with an office diastolic blood pressure between 105 and 130 mmHg. Patients underwent 24 hr ambulatory BP monitoring, 2 D and M-mode echocardiography for LV mass determination, and thirty minute resting supine blood tests for catecholamines and plasma renin activity (PRA).

	Women	Men	*p* (women vs men)
Office SBP	176 ± 5	177 ± 5	NS
24 hr SBP	155 ± 4	171 ± 6	<0.05
Office, 24 hr SBP	21 ± 4	6 ± 3	<0.05

There were no significant differences in age, known duration of hypertension, body mass index, ethnicity, or plasma lipids except for HDL cholesterol, which was higher in women. Office systolic and diastolic blood pressures did not differ between men and women; however, the difference between office systolic and 24 hr or daytime average ambulatory bp was significantly greater for women than for men ($P < 0.02$). In this group, a lower percent of women had LVH (which is a marker for hypertensive end-organ damage), and their PRA was significantly lower than that of the men. This suggests that for women with moderate to severe hypertension, the ambulatory pressures may better reflect overall cardiovascular risk.

2. **Effect of Blood Pressure Reduction on Coronary Flow Reserve in Essential Hypertension.** Joseph A. Diamond, Josef Machac, Milena Henzlova, Maria Ardeljan, Arlene Travis, Craig Wilkenfeld, Kevin L. Martin, Lawrence R. Krakoff, Robert A. Phillips. Mount Sinai School of Medicine, New York, New York.

Coronary flow reserve (CFR) is blunted in untreated essential hypertension. The effect of sustained blood pressure (BP) reduction on CFR needs to be understood.

Therefore, we examined the relation between BP reduction and CFR in 20 untreated hypertensive men without evidence of epicardial CAD. Coronary perfusion was evaluated at baseline and after maximal coronary vasodilatation with adenosine using split-dose quantitative thallium-201 imaging. The ratio of counts during maximum coronary vasodilation by adenosine divided by baseline counts in the anterior wall defined the CFR, a method validated with microspheres in dogs.

After a month of medical therapy, all patients had $\geq$15 mm Hg decrease in diastolic BP. As shown below, CFR varied in relation to Δ systolic BP, p value <0.01.

Δ Systolic BP (mm Hg)	↓ CFR	↑ CFR	Mean ΔCFR
Increase ($n = 4$)	4	0	−0.1 ± 0.1
Decrease 1–30 mm Hg ($n = 11$)	2	9	0.2 ± 0.3
Decrease >30 mm Hg ($n = 5$)	4	1	−0.2 ± 0.3

CFR improved only in the group with a 1 to 30 mm Hg reduction in systolic BP. Regression analysis suggested a U-curve relation between Δ systolic BP and Δ CFR.

Conclusion. There is an optimal range of systolic BP reduction in which CFR improves. These results suggest that excessive sustained reduction of systolic BP may be detrimental during treatment of hypertension.

3. **Quantitative Adenosine-Thallium Perfusion Imaging Assessing Coronary Flow Reserve in Arterial Hypertension.** Joseph A. Diamond, Josef Machac, Milena Henzlova, Maria Ardeljan, Arlene Travis, Craig Wilkenfeld, Kevin L. Martin, Lawrence R. Krakoff, Robert A. Phillips. Mount Sinai School of Medicine, New York, New York.

Invasive techniques and positron emission tomography have shown that coronary flow reserve (CFR) is reduced in left ventricular hypertrophy (LVH).

In humans we assessed the relation between LV mass and CFR using a new non-invasive method, quantitative adenosine thallium perfusion imaging, which we have recently validated by microspheres in a dog model. LV mass was determined by 2-D directed M-mode echocardiography in 18 untreated hypertensive men (age = 48 ± 7) without evidence of epicardial CAD. CFR was quantified by split-dose thallium-201 perfusion imaging. The ratio of counts during maximum coronary vasodilation by adenosine infusion divided by baseline counts defined CFR.

CFR was detected (ratio > 1.0) in the septal and anterior walls in all patients as shown:

	Mean ± SD	Range
CFR, anterior wall	1.5 ± 0.3	1.1—2.1
CFR, septal wall	1.7 ± 0.3	1.1—2.2

CFR in the anterior and septal walls was inversely related to LV mass ($r = -0.61$, $p < 0.01$, $r = -0.50$, $p < 0.03$, respectively). LVH was present in 67% of patients in the lower one-half range of CFR but in only 22% of patients in the upper one-half ($p = 0.05$).

Conclusion. This study confirms that CFR is reduced in hypertensive patients with LVH. This new non-invasive method for determining CFR may be used to identify patients at risk for abnormal coronary perfusion and is suitable for serial measurements to assess the effect of treatment on CFR.

4. Myocardial Viability Detection With Tc-99m Teboroxime. Milena J. Henzlova, Joseph A. Diamond, Josef Machac. Mount Sinai Medical Center, New York, NY.

Tc-99m Teboroxime is a newer myocardial perfusion imaging agent. Its utility for detection of myocardial viability is uncertain.

We studied 40 patients with chronic coronary artery disease (30M/10F, 64 ± 10 yrs). All underwent thallium-201 stress test with early (Tl-S), 4 hr (Tl-4), and 24 hr post-reinjection (Tl-24) SPECT imaging followed by rest (TEBO-R) and washout (TEBO-W) Teboroxime SPECT imaging. Tracer uptake was classified as normal, mildly, moderately or severely abnormal in 7 myocardial segments in all 5 sets of images.

TL-S images reveal 81 normal segments, 63 mild, 25 moderate and 99 severe defects. Number of segments with subsequent improvement was as follows:

	Mild	Moderate	Severe
	N (%)	N (%)	N (%)
T1–4	13 (21)	12 (48)	18 (19)
T1–24	26 (35)	15 (58)	38 (38)*
TEBO-R	28 (38)	15 (58)	25 (25)
TEBO-W	29 (41)	11 (48)	21 (25)

* $p = 0.05$ (T1–4 vs. T1–24).

Thus, there is close correlation between Tl-24 and TEBO-R for detection of viability and absence of additional information from TEBO-W images.

5. Vagal Tone Is an Important Modulating Factor on the Re-entrant Arrhythmic Substrate for the Genesis of Sustained Ventricular Tachycardia. Olle Kjellgren, MD, Kyung Suh, RN, J. Anthony Gomes, MD. Divisions of Cardiology at Beth Israel Medical Center & Mount Sinai Medical Center, NY.

The influence of vagal tone on the reentrant arrhythmic substrate for the genesis of sustained ventricular tachycardia remains unclear.

To assess the influence, we studied the heart rate variability (HRV) in 59 patients (coronary artery disease: 32, cardiomyopathy: 13, no structural heart disease: 14) that underwent invasive electrophysiological testing as well as signal-averaged electrocardiography (SAECG), 24 hour Holter monitoring and determination of left ventricular ejection fraction (LVEF). HRV was evaluated from 24 hour recordings by multiple time domain (SDRR, SDANN, SD, PNN50) and frequency domain (0.01–1.00 Hz (TP), 0.04–0.15 Hz (LFP), 0.15–0.40 Hz (HFP), Max & Min High Frequency Power during one hour) measures.

The patients with inducible sustained ventricular tachycardia ($n = 28$) were found to have lower HRV by all time and frequency domain measures over 24 hours when compared to the noninducible patients ($n = 31$); e.g. PNN50 (4 vs 9%, p 0.03) and HFP (9 vs 14 ms, p 0.02). MaxHFP 1 hr also differed (20 vs 27 ms, p 0.04) but not MinHFP 1 hr (5 vs 6 ms). HRV did not correlate with the SAECG, with high grade ventricular ectopy or with LVEF. The SAECG, but not the Holter or the LVEF, predicted inducibility of ventricular tachycardia (p 0.04).

Conclusions. (1) Parasympathetic tone does not correlate with the presence of late potentials, ventricular ectopy or left ventricular dysfunction. (2) Low mean as well as maximal vagal tone, in contrast to minimal vagal tone, predicts inducibility of ventricular tachycardia. (3) Thus, the inability to modulate vagal tone is an important determinant in the genesis of reentrant sustained ventricular tachycardia.

6. Relationship between Chest Pain following Successful Directional Coronary Atherectomy and Removal of Vascular Deep Wall Components. Adam L. Kushner, Samin K. Sharma, Douglas H. Israel, Thomas Cocke, Billie Fyfe, Kirk McMurtry, Jonathan D. Marmur, Sabino R. Torre, John A. Ambrose. Department of Cardiology, Mt. Sinai Medical Center, New York, NY.

Post procedure chest pain (PPCP), defined as pain lasting for more than 5 minutes, following successful percutaneous coronary revascularization often indicates acute or threatened closure with patients often returning to the cardiac cath lab. Part of the mechanism of directional coronary atherectomy (DCA) involves the removal of atheromatous material via a rotating blade. Previous experience with this device has suggested that cutting vascular deep wall components (media, adventitia) may result in chest pain, although clear evidence for this hypothesis is lacking.

Purpose. To determine if removal of deep wall components (DWC) during DCA can cause PPCP following a successful procedure.

Methods. Only patients with single target lesions following successful DCA were included in this analysis. Successful procedures were defined by retrieval of atheromatous material, with a greater than 20% reduction in initial stenosis and a final residual stenosis of less than 50%. Atheromatous tissue removed during DCA then underwent histopathological analysis for identification of DWC. Patients with PPCP and EKG changes following DCA were encouraged to return to the cardiac cath lab for repeat angiography.

Results. DCA was successful in 172 patients with single lesions. PPCP occurred in 24% of patients (42/172) and removal of DWC occurred in 27% of lesions (47/172).

	DWC +	DWC −	
PPCP +	29*	13	*$p < 0.0001$
PPCP −	18	112	

Nineteen percent of patients with PPCP (8/42) had T-wave changes on their EKG and 2 patients had S-T segment elevation. 10 patients returned to the cath lab for repeat angiography. All 8 patients with only T-wave changes had widely patent vessels, while the 2 patients with S-T segment elevations had acute or threatened vessel closure.

Conclusion. Removal of vascular DWC following successful DCA is often associated with PPCP despite a patent vessel on repeat angiography. T-wave changes alone appear to have a low predictive value for vessel reclosure and repeat angiography for PPCP after successful DCA may not be warranted in the absence of S-T segment changes.

7. Is the Relation between Insulin Sensitivity and Blood Pressure in Women Unique to Hypertensives? Kevin L. Martin, Maria Ardeljan, Diane T. Finegood, Sebastian Zimmerman, Lawrence R. Krakoff, Robert A. Phillips. Mount Sinai School of Medicine, New York, New York.

To better understand the relation between blood pressure (BP) and insulin sensitivity in women ⩽ age 50, fifteen normal controls and eight borderline hypertensive patients of similar age and body mass index (29.4 ± 6.4 vs. 28.6 ± 9.7 kg/m^2, respectively) were studied. Insulin sensitivity index (S_I) was assessed with the frequently sampled intravenous glucose tolerance test using the minimal model.

The average BP in hypertensives was 144/93 mm Hg and 120/76 mm Hg in controls ($p < 0.0001$). Despite different BP, S_I was similar (4.3 ± 2.9 vs. $4.2 \pm 2.7 \times 10^{-4}$ min^{-1}/uU/ml, p = ns), as was the relation between systolic BP and S_I. For every unit decrease in S_I systolic BP increased 2.6 mm Hg in hypertensives ($r = 0.56$, $p < 0.03$) and 2.3 mm Hg in controls ($r = 0.72$, $p < 0.05$).

This study suggests that the effect of insulin resistance on BP in women is not unique to hypertensive subjects. Measures which improve insulin sensitivity in normotensive women may prevent future blood pressure elevation.

Clinical Immunology

8. Regulatory Effects of Immunoglobulin on Human B Cells. Charlotte Cunningham-Rundles, Zhuo Zhou and Lloyd Mayer. Division of Clinical Immunology, Mount Sinai Medical Center, One Gustave Levy Place, New York, NY 10029.

Intravenous immunoglobulin (IVIg) derived from pooled human serum is an expensive biologic unexpectedly found to ameliorate, or even cure, certain autoimmune diseases. While certain facets of these "immunomodulating activities" are understood, many questions remain. Ongoing work in our laboratory has focussed upon factors which regulate human B cell growth and differentiation. In the course of this work we previously found that polyspecific pooled human IgG isolated from IVIg could inhibit pokeweed mitogen induced immunoglobulin production by normal B cells, in a dose-dependent fashion. These effects were primarily directed at inhibition of B cell maturation, and less so for B cell proliferation. Monomeric IgG derived from IVIg was also found inhibiting to induction of B cell differentiation by factors derived from T cell hybridomas. More recently we have identified and biochemically defined a normal human B cell differentiation factor, (446-BCDF), which is a potent inducer of Ig secretion in activated B cells.

As expected from our other work, Ig from IVIg was found to inhibit profoundly 446-BCDF driven B cell differentiation. In addition to these effects on human peripheral B cells, polyclonal IgG also inhibits by 90% the stimulating effects of IL-6 on CESS, an IgG lambda producing B cell line and polyclonal IgG inhibits autoantibody secretion of 2 clonal human cell lines which secrete rheumatoid factors. These immunomodulating functions are evidently properties of both Fab and Fc portions since neither antibody fragment alone inhibits as well as the intact Ig molecule. To determine the mechanism(s) of inhibition of B cell differentiation by IVIg, we have postulated three mechanisms: (1) Fc receptor crosslinking resulting in inhibition, (2) the presence of anti-idiotypic, anti-allotypic, or anti-DR (or HLA) antibodies in IVIg or (3) the presence of antibodies in IVIg to B cell differentiation factors or their receptors.

The effects of IVIg in vivo are likely to be complex. Only by dissecting the specific actions of IVIg on human B cells in well-defined systems can the therapeutic role of IVIg in autoimmune disease be clarified.

9. Effect of Low Dose Oral Interferon Alpha-N3 (IFN) in ARC. J Hassett and L Mendelsohn. Division of Clinical Immunology, Mount Sinai School of Medicine, NY, NY 10029 USA.

We evaluated low dose oral interferon in symptomatic ARC patients (pts) with initial CD4 counts 100–350 mm^{-3} because previous animal and human studies had suggested activity of alpha interferon by this route.

In the initial, double-blind phase, pts received either interferon alfa-n3 (Human Leukocyte Derived, Interferon Sciences, Inc., New Brunswick, NJ, USA) (IFN) 150 IU/day or placebo (PLA) for 6 weeks, followed by a 4 week rest period. Pts were eligible to continue in an open study on IFN 150 IU/day for up to 48 additional weeks. Of 41 pts entered, 24 were receiving AZT, evenly distributed between treatment groups. Twenty-three pts were randomized to receive IFN and 18 to PLA for the initial phase; 36 entered the open phase.

No adverse events related to IFN were noted. In the randomized phase, there were no significant differences between IFN and PLA groups in baseline ((193 ± 67 vs 222 ± 77 mm^{-3}) or changes (−30 ± 36 vs −13 ± 47) in CD4 count. Weight change, incidence of fever and prevalence of thrush did not differ significantly between treatment groups. Prevalence and severity of common symptoms, such as anorexia and fatigue, improved more in the IFN (11.8%) than PLA (5.6%) group during the randomized phase (p = .02, two sample ANOVA T-test). In the open phase of the study, CD4 counts declined a mean of 8 mm^{-3}/mo. In a total of 23.3 pt-yrs of IFN treatment, only one pt progressed to AIDS, as manifest by development of a lymphoma at week 42. Mean weight change over the course of the study was minimal, −0.5 kg at week 34 and −0.9 kg at week 58. During the open phase, symptomatic improvement was maintained by those pts who received IFN and achieved by those who received PLA during the randomized phase.

While oral IFN at the dose and schedule used does not appear to affect CD4 counts, it may improve symptomatology, and prevent or delay progression to AIDS.

10. CD40 Crosslinking in the Presence of Staphylococcus Aureus Cowan I Strain Organisms (SAC) Stimulates Polyclonal Human B Cell Differentiation. R. Huang, S. M. Fu, and L. Mayer. Department of Medicine, Mount Sinai Medical Center, New York, NY 10029 and University of Virginia, Charlottesville, VA.

Crosslinking of CD40 on murine and human B cells has been shown to be effective in generating long term B cell lines, inducing B cell proliferation, IgE secretion in the presence of IL4. However, CD40 crosslinking alone is not sufficient, suggesting that the nature of the costimulatory signal may be important in the final outcome.

Since SAC is a recognized costimulatory signal for both B cell growth and differentiation factors, we cocultured isolated human peripheral blood B cells with SAC (0.001% v/v) and anti-CD40 mAb 626.1.

Most of the B cell preparations responded to this combination of signals with more than 5 fold increase in Ig secretion. This response was polyclonal with secretion of IgM, IgG, and IgA, and could be enhanced with IL2 and 446-BCDF. We then utilized 2 EBV-transformed B cell lines which constitutively express CD40, CESS (IgG1) and SKW (IgM). In the presence or absence of SAC, anti-CD40 induced minimal increases in IgG in CESS cells and SKW failed to secrete any Ig. The level of stimulation seen in CESS cells was significantly lower than that induced by IL6.

Thus, CD40 may be an important costimulatory signal for B cell differentiation but clearly requires a second cytokine for optimal effects.

11. Cytokine Secretion Profile Relates to the Initial Activation Stimulus. K. Kazbay and L. Mayer. Division of Clinical Immunology, Mount Sinai Hospital, N.Y.

Several reports have indirectly suggested that cytokine secretion by T cells may be altered by the initial activation signal. We have previously reported that peripheral blood T cell stimulation with an anti-CD3ε chain mAb (mAb-454) induces IL2 secretion but no B cell differentiation factor (BCDF) activity, while anti-CD3γ chain stimulation (mAb-446) induces BCDF but no IL-2 secretion. Both mAbs were equally effective in inducing proliferation of T cells and secretion of BCGF, IL-4 and γ IFN.

To determine whether the dichotomy between BCDF and IL-2 secretion was due to activation of distinct T cell subpopulations or differential activation of the same T cells, we generated T cell clones from mAb-446 and 454 stimulated T cells by limiting dilution and then restimulated them with either mAb 454 or 446.

Proliferation of the T cell clones and secretion of BCGF were comparable after restimulation with either mAb. However, regardless of the initial activation signal, mAb 454 induced IL-2 and no BCDF secretion and mAb 446 stimulated BCDF and no IL-2 secretion.

These data strongly support the concept that the mechanism of T cell activation dictates the cytokine secretion profile. These findings may have significant implications with regard to the concept of Th1/Th2 clones.

12. Maintenance of In Vitro Anergy in T Cells by the Persistence of Stimulation. K. Kazbay and L. Mayer, Division of Clinical Immunology, N.Y.

Although tolerance to the self-antigens is mainly induced in the thymus, there are also peripheral mechanisms, clonal deletion or anergy. Recently, we have been able to induce an anergy in human peripheral T cells by stimulation with anti-CD3ε and anti-CD3γ mABS.

The anergy was cross-reactive, complete (total inhibition of proliferation; IL2, IL6, BCDF and BCGF secretion), and the CD3 complex was not modulated. Co-stimulation with anti-CD28, anti-CD2 or γ-IFN, or co-culturing in the presence of allogenic APCs or heat shocked self-APCs did not prevent the induction of anergy.

Anergic cells were able to proliferate with exogenous IL2 or PHA. Cells remained anergic as long as anti-CD3 mAbs were maintained in the culture medium. Interestingly, when both CD3 and exogenous IL2 were removed from the culture medium, T cells demonstrated an almost complete recovery within 4–6 days for anti-CD3 stimulation (proliferation and cytokine secretion) while their proliferative responses to IL2 declined. On the other hand, maintaining the cells in the exogenous IL2 without anti-CD3 mAbs kept them responsive to IL2 stimulation but greatly inhibited the recovery for CD3 stimulation.

These findings suggest that anergy in T cells can be maintained with the continuous presence of CD3-TCR stimulation, but recovery may occur in the absence of exogenous signals.

13. Selective Versus Global Cytokine Secretion Defects in Common Variable Immunodeficiency. K. Kazbay, C. Cunningham-Rundles, and L. Mayer. Division of Clinical Immunology, Mount Sinai Hospital, N.Y.

Common variable immunodeficiency is a heterogeneous disorder characterized by absent, low, or ineffective antibody secretion in vivo. To date, a number of in vitro defects have been described to explain the general lack of antibody defects, absence of T cell help, and excessive T cell suppression. We analyzed a panel of CVI patients (N = 34) and normal healthy controls (N = 27) for their in vitro T and B cell function. Previously we have shown that B cells from the majority of these patients (89%) can respond in vitro to isolated B cell differentiation factors (BCDF) with normal or near normal levels of Ig secretion, while the majority (71%) of patients failed to secrete this factor.

In order to determine whether the failure to secrete BCDF was a selective defect, we measured BCGF, IL2 and IL6. BCGF secretion after either PHA or anti-CD3 stimulation.

In some patients the effect was global for all three cytokines (17%), while in the remainder, the defects were more selective. IL-2 deficiency did not appear to correlate with BCDF deficiency, however, in no case was IL-6 deficiency present without BCDF deficiency. Selective BCDF deficiency was present in 17% of patients. In another 17% of patients all 3 cytokine were found to be in normal range, indicating the defect may reside elsewhere.

These data suggest that CVI may result from defects in cytokine secretion which may act on different stages of B cell differentiation.

14. Purification to Homogeneity of a Novel Human B Cell Differentiation Factor. Y. Kuang, L. Mayer. Division of Clinical Immunology, Mount Sinai Medical Center, N.Y.

We have previously described a potent human B cell differentiation factor, 446-BCDF, derived from anti-CD3 stimulated peripheral blood T cells, which induced a 5–100 fold increase in Ig secretion by PB B lymphocytes. This cytokine does not possess activity consistent with either IL-2, IL-4, IL-6 or IL-10 in cytokine specific assays.

mAb were generated against a partially purified 446-BCDF preparation. One mAb, 929, specifically inhibited 446-BCDF activity without any effects on IL-2 or IL-6 induced B cell differentiation. mAb 929 was covalently coupled to CNBr activated Sepharose 4B beads and used an affinity column. Passage of 446-BCDF over this column removed activity (effluent) and elution (0.1 M glycine-HCL) restored it. PB T cells were then labelled with ^{35}S methionine and cysteine and stimulated with anti-CD3 mAb 446 for 20 h. Supernatants were passed over the 929 affinity column, eluted fractions were precipitated with 10% TCA, and loaded onto SDS-PAGE.

While the effluent contained many bands, the column eluate revealed one band at a molecular weight of 44kD consistent with the previously determined MW for this cytokine.

Thus we have purified a novel human B cell differentiation factor 446-BCDF to homogeneity and documented its unique activities.

15. CD8 Crosslinking Is Necessary but not Sufficient for CD8$^+$ T Cell Activation by Normal Intestinal Epithelial Cells. Y. Li and L. Mayer. Division of Clinical Immunology, Mount Sinai Hospital, N.Y.

The activation of CD8$^+$ T cells by normal intestinal epithelial cells (IEC) in mixed lymphocyte culture has significant implications for the regulation of mucosal immune responses. We have previously shown that the CD8 molecule itself may be playing a role in this process since anti-CD8 mAbs inhibit IEC driven CD8$^+$ T cell proliferation and coculture of IEC with T cells results in the activation of the src-like tyrosine kinase p56lck associated with the intracytoplasmic tail of the alpha chain of CD8.

In order to determine whether CD8 crosslinking alone is sufficient for CD8$^+$ T cell proliferation, we added anti-CD8 mAbs to peripheral blood T cells and crosslinked them by the addition of goat anti-mouse IgG antibody.

While we were able to detect the induction of p56lck, no proliferation was noted. Addition of cytokines (IL-2, IL-6 or mixed lymphocyte culture supernatants) to these cultures also failed to promote proliferation, suggesting that IEC were providing additional signals, other than the crosslinking CD8 and accessory cutokines, to induce proliferation. In order to determine whether crosslinking CD8 was in fact an important event, we added genestein, a tyrosine kinase inhibitor, to the T cell:IEC cultures. Preincubation for 2 h was sufficient to shut down the CD8$^+$ T cell proliferative response, providing evidence that CD8 crosslinking was an important early event in IEC driven CD8$^+$ T cell proliferation.

These findings suggest that additional signals, most likely conate interactions (?TcR mediated) are important in mucosal immunoregulation by IEC.

17. Expression and Regulation of Cytokine Receptors on Intestinal Epithelial Cells from Normal Controls and Patients with IBD. A. Panja, S. Goldberg, and L. Mayer. Division of Clinical Immunology. The Mount Sinai Medical Center, New York, N.Y.

Products of an activated immune system may affect cells within the immune system as well as nonlymphoid cells in the local environment. Given the activated state of the intestinal tract it is conceivable that local cytokines generated could regulate epithelial cell function. In order to assess whether epithelial cells are targets for particular cytokines, we initiated studies on the expression and regulation of receptors for a panel of proinflammatory cytokines in freshly isolated epithelial cells from normal and IBD patients.

Intestinal epithelial cells (IEC) were isolated from surgical specimens (control NL n = 9, UC inv n = 9, UC uninv n = 1, CD inv n = 4, CD uninv n = 5) by dispase treatment. Cells were stained with phycoerythrin conjugated cytokine to determine receptor expression and density for IL-1β, IL-6, GM-CSF and TNFα by flow cytometry and fluorescence microscopy.

Receptors (R) for IL-1β, IL-6 and GM-CSF were readily detectable (GM-CSFR $\gg$ IL-1βR > IL-6R) in all epithelial cell preparations at levels lower than the levels that occurred on conventional antigen presenting cells (APCs). No significant differences were seen between normal and IBD epithelial cells for IL-1βR or IL-6R, whereas receptors for GM-CSFR was decreased in inflamed IEC when compared to uninflamed or normal control IEC. GM-CSF R could be upregulated in epithelial cell lines by PMA but not by LPS or γIFN. IL-6R was down regulated by LPS and upregulated by IL-1β consistent with receptor regulation in monocytes. TNFα receptors were neither detectable nor inducible in epithelial cells from normal or IBD patients.

These results suggest that cytokine receptor expression on professional and nonprofessional APCs are comparable and that the epithelial cells have the potential to be regulated by proinflammatory cytokines.

18. Synthesis and Regulation of Accessory Cytokines in Human Intestinal Epithelial Cells: Comparison between Normal and IBD. A. Panja, E. Siden, S. Goldberg, and L. Mayer. Division of Clinical Immunology, The Mount Sinai Medical Center, New York, N.Y.

Intestinal epithelial cells (IEC) are unique in their ability to act as antigen presenting cells (APC) in vitro and may also have this capacity in the intestinal environment. Unlike conventional APCs, normal IEC selectively stimulate CD8$^+$ peripheral blood T cells to proliferate in mixed lymphocyte culture. We have previously reported that normal IEC express a profile of cytokine mRNAs distinct from conventional APCs (low level constitutive IL-6 expression but no detectable IL-1β, TGFβ or TNFα).

To determine whether cytokine secretion correlated with mRNA or whether induction of TNF or IL-1 was possible, we isolated IEC from normal or IBD surgical specimens and cultured them alone or in the presence of lipopolysaccharide (LPS) or gamma-interferon (γIFN). Induction of mRNA was assessed by RNAase protection while protein secretion was measured by ELISA (IL-1) or bioassay (TNF and IL-6) of culture supernatants of purified epithelial cells.

All IEC spontaneously secreted levels of IL-6 comparable to that of LPS-treated macrophages, although IEC isolated from inflamed UC tissues elaborated even more. Using the RNAase protection assay, IEC IL-6 mRNA also increased approximately 200-fold during the first 24 hours of culture.

TNF bioactivity was detectable in only a limited number of samples. Neither LPS nor γIFN resulted in the secretion of IL-1 or TNF and had no effect on spontaneous IL-6 production. These data support and extend our previous findings but do not support a role for IEC-derived proinflammatory cytokines in IBD.

19. Altered T Cell Signal Transduction in Parental Tumor Bearing Mice Is Prevented by Tumor Derived-IL-2. S. Salvador,* A. Pizzimenti,* B. Gansbacher,** and K. S. Zier.* *Division of Clinical Immunology, Department of Medicine, Mount Sinai School of Medicine, N.Y.; **Department of Hematologic Oncology, Memorial-Sloan Kettering Cancer Center, N.Y.

Although the immune system is able to fight foreign pathogens successfully, the rejection of spontaneous tumors often cannot be achieved. To increase the recognition by the immune system, the murine fibrosarcoma CMS5 was transduced with the interleukin-2 (IL2) gene. While animals inoculated with 0.25×10^6 parental CMS5 cells died in approximately 40 days, those injected with the IL-2 secreting developed slow growing tumors and survived for longer than 100 days. To explore the molecular basis of the differences between parental tumor bearing (PTB) and IL-2 secreting tumor bearing (ITB) mice, biochemical events that follow T cell activation have been investigated.

The T cell receptor (TcR)/CD3 complex is a cell surface structure responsible for the recognition of foreign antigens. Splenocytes from PTB and ITB were enriched for T cells which were then activated for different lengths of time by crosslinking surface CD3. First, we examined the phosphorylation of tyrosine residues, since this is among the earliest events that follow TcR occupancy. T cells from PTB showed a different pattern of phosphorylated substrates compared to T cells from ITB or naive animals, including additional bands not seen in material from ITB or naive mice. Second, the expression of p56^{lck} and p59^{fyn} tyrosine kinases was investigated, since these enzymes responsible for protein phosphorylation are associated with the TcR. Neither was seen in cells from PTB mice, whereas they were readily detected in lysates from ITB mice. Third, we studied the expression of the chain of the TcR, since it has been shown to transduce activation signals following ligand binding and found decreased levels in material from PTB compared to that from ITB mice. Finally, Ca^{++} flux in stimulated cells was investigated and revealed that cells from PTB mice had decreased Ca^{++} mobilization compared to ITB mice.

Taken together, these results demonstrate profound metabolic impairment in T cell from PTB mice that might be responsible, at least in part, for their lack of tumor rejection. They suggest also that the IL-2 secreted by the tumor may influence the development of these abnormalities.

20. Antigen Uptake and Trafficking in Human Intestinal Epithelial Cells. A. L. So, K. Pelton-Henrion, G. Small, and L. Mayer. Division of Clinical Immunology, Departments of Medicine, Microbiology, and Cell Biology, Mount Sinai Medical Center, N.Y.

Intestinal epithelial cells (IECs) have been shown to function as antigen presenting cells (APCs) in gut mucosal immune responses. Intestinal epithelial cells express low levels of major histocompatibility complex (MHC) class II antigens and are capable of presenting soluble antigens to stimulate MHC-restricted antigen primed T cells. However, little is known about the uptake, processing and presentation of antigens by these unconventional antigen presenting cells. Hence, it would be of interest to contrast the pathway(s) that intestinal epithelial cells employ to handle antigens with those of conventional APCs.

Human colorectal adenocarcinoma cell lines (e.g. HT29, Caco-2, DLD-1) were used as model systems to study the APC properties of IECs. The kinetics of antigen uptake was performed using fluorescence microscopy to follow fluorescein (FITC) labeled antigens (e.g. tetanus toxoid (TT), transferrin (TF)).

Whereas in macrophages, intracellular punctate staining of FITC-TT was evident after 5' of incubation at 37°C, in HT29, intracellular staining of FITC-TT was not evident until after 30' of incubation. These results were confirmed by both confocal and electron microscopy (using colloidal gold-labeled TT). Internalized gold-labeled TT was found in endosomes and multivesicular bodies but not in the lysosomal compartments by 60'. Chloroquine (1 mM × 1 h), which inhibits receptor-mediated endocytosis, was used to pretreat HT29 cells. Little effect on the uptake of FITC-TT was observed, but there was inhibition of FITC-TF uptake.

Taken together, the uptake of FITC-TT by intestinal epithelial cells is non-receptor-mediated with kinetics slower than conventional APCs. Endosomes and multivesicular bodies could be the potential sites where antigens (e.g. TT) are processed and complexed with MHC class II molecules.

Endocrinology

23. Overestimation of Low Concentrations of hTSH in a 3rd Generation Immunoassay. E. Diamond, L. Miller, M. Valentine. Division of Endocrinology and Metabolism, Mount Sinai School of Medicine, NY, NY.

Sensitive hTSH assays permit discrimination between euthyroid and hyperthyroid individuals, are useful in monitoring thyroid hormone replacement therapy and as a result can be used as first line tests for thyroid dysfunction. We compared the ability of two 3rd generation hTSH assays (reported sensitivity to 0.01 uU/mL) to measure low concentrations of hTSH.

Both systems are solid phase two site chemiluminometric assays utilizing polystyrene beads coated with capture antibody. The IM-TSH (Immulite automated assay) uses an enzymatic reaction to produce prolonged luminescence whereas in the N-TSH (conventional, manual assay) oxidation of the chemiluminescent label produces an instantaneous light flash.

Circulating hTSH concentrations in 126 euthyroid individuals ranged from 0.10–5.7 uU/mL in the N-TSH assay and 0.06–4.2 in the IM-TSH system. Functional sensitivity (TSH concentration at which the between-assay % coefficient of variation is 20%) was estimated for both assays from precision-dose profiles using over 250 duplicate analyses of patient samples, standards, controls and dilutions of hTSH preparations run in over 10 different assays. These data show that the IM-TSH assay had a functional sensitivity of 0.005 uU/mL whereas the N-TSH was 3-fold less sensitive at 0.015 uU/mL. Serial dilutions of known amounts of pituitary and recombinant hTSH were prepared and assayed over the normal and subnormal range.

Both methods gave similar results, however, at known concentrations of pituitary and recombinant hTSH below 0.3 uU/mL the N-TSH method consistently overestimated the concentrations of hTSH added. These studies suggest that the automated system (Immulite) with its prolonged light reaction more accurately measures subnormal concentrations of hTSH and is the more sensitive of the two assay methods.

24. Exendin-4 Is a Potential Therapeutic Agent for Type 2 Diabetes Mellitus. John Eng, Valerie Gutterman, and Carlo Nicolis. Division of Endocrinology, Veterans Affairs Medical Center, Bronx, NY, and Mount Sinai School of Medicine, NY, NY.*

There is accumulating evidence that tight diabetic control will delay or possibly prevent the occurrence of diabetic complications. However, use of insulin or sulfonylureas to achieve tight glucose control increases the frequency of hypoglycemic events. GLP-1 (glucagon-like peptide I) has been demonstrated to be clinically useful in the treatment of type 2 diabetes mellitus (N. Engl. J. Med. 326:1316–1322, 1992). It is a glucose-dependent insulinotropin that avoids the side effect of hypoglycemia: it stimulates endogenous insulin secretion in the presence of hyperglycemia but has reduced or no insulinotropic activity under euglycemic or hypoglycemic conditions, respectively. In addition, GLP-1 inhibits glucagon secretion which further aids in glucose disposal by decreasing hepatic glucose production. We now demonstrate that exendin-4, a recently discovered peptide with 50% homology to GLP-1 (Mt. Sinai J. Med. 59:147–149, 1992), a) acts through GLP-1 receptors to stimulate insulin secretion and b) acutely lowers hyperglycemia in an animal model with type 2 diabetes.

Exendin-4 and GLP-1 (0.2–0.5 nmol) were administered as intravenous boluses to fasted conscious dogs either separately or in combination with the exendin inhibitor, exendin(9-39)amide (J. Biol. Chem. 267:21432–21437, 1992). Exendin-4 is 3–5 fold more potent than GLP-1 at stimulating insulin secretion in dogs.

Exendin(9-39)amide inhibited the insulinotropic response to both exendin-4 and GLP-1 by 70–90% as measured by area under the curve for insulin response over 30 minutes. The inhibition indicates that exendin-4 and GLP-1 act through a common receptor on pancreatic beta cells to stimulate insulin release and that exendin-4 is likely to have a spectrum of biological activities similar to GLP-1. Exendin-4 was tested in the db/db mouse, an animal model which displays obesity, hyperglycemia and hyperinsulinemia, all characteristics of type 2 diabetes mellitus. Exendin-4 (1 μg/g body weight) was given intraperitoneally to five db/db mice and orbital sinus blood sampled at 0 and 60 minutes. Blood glucose decreased from 310 ± 37 mg/dL at time 0 to 181 ± 37 at 60 minutes.

We conclude that exendin-4 is an insulinotropic agent that has potential use as treatment for type 2 diabetes mellitus.

25. Tissue Characterization of a Human TSH Receptor Variant Protein. P. N. Graves, P. Fong and T. F. Davies. Division of Endocrinology & Metabolism, Department of Medicine, Mount Sinai School of Medicine, New York, NY.

We have shown that the major variant of the human TSH receptor (hTSHR) mRNA is 1.3 kb (hTSHR-v1.3). This mRNA encodes a protein of 253 amino acids incorporating 231 amino acids co-linear with the extracellular N-terminus of the holoreceptor followed by 22 amino acids not present in the natural sequence hTSHR mRNA (Biochem Biophys Res Comm 1992; 187:1135). This hTSHR-v1.3 mRNA was identified in normal and abnormal human thyroid tissue but in no other human tissues examined. Quantitatively, approximately 30% of all hTSHR-related mRNAs were v1.3.

To identify the v1.3 translation product, rabbit polyclonal antisera were raised to the last 11 amino acids of the unique carboxy terminus and to amino acids 16–50 of the N-terminal extracellular region. The specificity of these antisera was demonstrated by expressing v1.3 cDNA in *E. coli* and baculovirus expression systems followed by Western blot analysis.

In the bacterial system, both antisera recognized a predicted 32 kd protein while also recognizing a glycosylated 69 kd secreted protein from recombinant baculovirus infected Sf9 insect cells. In order to identify natural hTSHR-v1.3 protein we used the same antisera and found that they recognized a 69 kd protein in both normal and abnormal human thyroid tissue extracts. This 69 kd product was similarly identified by the rabbit antisera raised to the amino-terminal sequence of the natural hTSHR but not by several control rabbit antisera. There appeared to be no wide differences in the quantity of hTSHR-v1.3 protein in normal and autoimmune thyroids.

Identification of novel hTSHR variants raises the possibility that TSHR variant proteins may be important modulators of the autoimmune response to the hTSHR in Graves' disease.

26. **Posttransplantation Diabetes in Liver Transplant Recipients Is Associated with Hepatitis C-Induced Liver Disease.** H. Knobler, A. Stagnaro-Green, A. Carroccio, M. E. Schwartz, C. M. Miller, S. H. Roman. Departments of Medicine and Surgery, Mount Sinai School of Medicine, N.Y.

Diabetes mellitus (DM) is well documented in patients with cirrhosis. Liver transplantation is associated with posttransplantation DM (PTDM), although limited data report a low incidence.

We have followed up to 1 year the glucose tolerance of 52 liver transplant recipients who took part in a randomized trial comparing immunosuppressive therapy with FK 506 or cyclosporin A (CysA). An OGTT was performed pre, and at 6 & 12 months posttransplantation.

Eleven patients (23%) developed PTDM; five patients (10%) had DM prior to transplantation and their diabetes persisted posttransplantation. The risk for developing PTDM was significantly associated with the etiology of the liver disease: 8/13 (62%) patients with hepatitis C-induced liver disease developed PTDM, whereas only 2/15 (13%) with cholestatic liver disease ($p = 0.02$) and 1/19 (5%) patients with other causes of liver disease developed PTDM ($p = 0.0009$). Gender, age, BMI, and impaired pretransplantation OGTT were not significantly associated with PTDM. Patients with PTDM tended to have more episodes of liver rejection (2.2 vs. 1.1; $p = 0.001$) and therefore received more steroid cycles. At 6 months follow-up they had significantly lower serum albumin levels. There was no difference in the incidence of PTDM between the CysA and the FK 506 treatment groups, and also no correlation with these drug levels.

We conclude that diabetes is a common complication of liver transplantation, and that it occurs more commonly in patients with a high number of rejections, low serum albumin, and hepatitis C-induced liver disease.

27. **Detection, Localization and Hormonal Regulation of the Messenger RNAs for Estrogen Receptor, Insulin-Like Growth Factor II and Transforming Growth Factor Beta-3 in the Human Prostate.** A. C. Levine, M. Ren, and A. Kirschenbaum. Departments of Urology and Medicine, Mount Sinai School of Medicine, CUNY, New York, NY 10029.

The present study was undertaken to detect and localize the messenger RNAs (mRNAs) for the estrogen receptor (ER), insulin-like growth factor II (IGF-II) and transforming growth factor beta-3 ($TGFB_3$) in human prostate tissue and to study their regulation after treatment with a long-acting gonadotropin releasing hormone agonist (GnRHa).

A total of 9 prostate samples were taken from benign prostatic hypertrophy (BPH) areas of radical prostatectomy specimens performed for prostate cancer. 4/9 patients had prior treatment with a GnRHa ± an antiandrogen. ER and growth factor mRNAs were quantitated via RNAse protection assay. ER mRNA was localized via the combined techniques of in situ hybridization (ER mRNA) and immunocytochemistry utilizing anti-cytokeratin 903 antibodies which selectively stain prostatic basal epithelial cells.

The full-length ER mRNA was expressed in the prostate. Comparison of ER mRNA levels in GnRHa-treated vs. non-treated BPH areas showed significant upregulation of ER mRNA expression with GnRHa treatment. In situ hybridization combined with immunocytochemistry demonstrated that the greatest ER mRNA expression was in the prostatic basal epithelial cells. IGF-II mRNA expression was also increased in the 4 patients treated with GnRHa. The expression of $TGF\text{-}Beta_3$ did not increase with GnRHa treatment and did not correlate with histologic grade of the adjacent cancer.

We conclude that ER mRNA is expressed in the human prostate, primarily in prostatic basal epithelial cells and that the ER expression, as well as IGF-II expression, is increased with GnRH analogue therapy.

28. **Restricted Intrathyroidal T Cell Receptor V Gene Use in Murine Thyroiditis Is Reflective of Thyroglobulin-Reactive T Cells.** N. Matsuoaka, P. Unger,† and T. F. Davies. Division of Endocrinology and Metabolism, Dept. of Medicine and the Dept. of Pathology,† Mount Sinai School of Medicine, New York, NY.

Female CBA/J mice ($n = 10$) were immunized with human thyroglobulin (hTg) and histological autoimmune thyroiditis was observed in 9 mice 5 weeks after their initial immunization. The murine thyroid glands were removed and total cellular RNA prepared and reverse transcribed as target cDNA for polymerase chain reactions to detect 17 murine T cell receptor (mTcR) Vβ gene families.

Southern analysis of the resulting PCR fragments showed a remarkable bias in the use of certain mTcR gene families, in particular Vβ1, Vβ2 and Vβ13. Four T cell lines derived from lymph nodes or spleen cells were also established from similar mice 10 days after hTg immunization. These lines had hTg-induced stimulation indices of 5.9 to 13.0. Murine TcR Vβ gene family analysis of the lines showed the biased use of the same mTcR Vβ gene families as observed within the thyroiditis tissues. Each of the lines showed predominant use of at least 2 of the Vβ1, Vβ2, and Vβ13 gene families seen to be active within the thyroid glands of the mice with thyroiditis.

These data indicated that mTcR V gene analysis of intact thyroid tissue accurately reflected the thyroid antigen-specific T cells infiltrating the thyroid gland early in the development of thyroiditis. Furthermore, at least 3 Vβ gene families were identified in the T cell recognition of Tg in the context of $H\text{-}2^k$.

29. **Opioidergic Modulation and β-Endorphin Immunoreactive Innervation of Preoptic Area Brain Grafts in Hypogonadal Mice.** Gregory M. Miller, Ann-Judith Silverman and Marie J. Gibson. Division of Endocrinology, Mount Sinai School of Medicine, NY, NY, 10029, and Department of Anatomy and Cell Biology, Columbia University College of Physicians and Surgeons, NY, NY, 10032.

HPG mice are deficient in gonadotropin-releasing hormone (GnRH) and are infertile. When fetal preoptic area (POA) tissue is placed into the IIIV of adult HPG hosts, GnRH neurons in the graft target the median eminence and initiate reproductive development. We have previously shown that N-methyl-D,L-aspartic acid (NMA) stimulates LH secretion in female HPG/POA (Endocrin. 128:2432, '91). This study tested whether endogenous opioids interact with NMA to affect grafted GnRH neurons and/or terminals in female HPG/POA, and whether opiodergic effects on the GnRH system correlate with the presence of host-derived β-endorphin-like immunoreactive fibers within the graft.

Catheterized female HPG/POA were challenged with naloxone (NAL), NAL methiodide (NALMI) (which does not cross the blood-brain barrier), or saline, alone and in combination with NMA. LH was measured in sequential plasma samples by RIA.

β-endorphin immunoreactive fiber innervation of host origin was observed in all grafts examined. Similar to our findings in normal mice, NAL and NALMI failed to stimulate LH release, yet NAL significantly potentiated NMA-stimulated LH release in female HPG/POA.

We hypothesize that NMA stimulates the release of endogenous opioid peptides which interact with neuronal elements within the transplant to modify GnRH release.

Support: NIH Grants T32DK07645 (GMM) & HD19077 (MJG).

30. **Osteomyelitis Is a Marker for Accelerated Microvascular Disease in Patients with Diabetic Foot Ulcers: Results of a 3-Year Follow-Up Study.** L. G. Newman, S. H. Roman, and A. Stagnaro-Green. Department of Medicine, Mount Sinai School of Medicine, N.Y.

The natural history of patients treated for neuropathic diabetic foot ulcers (DU) is unknown. We performed a follow-up study of 24 patients with 30 ulcers, 8 without and 22 with underlying osteomyelitis (OM) documented by bone biopsy. OM was clinically unsuspected in 73% (16/22). Follow-up analysis assessed for the development of retinopathy, nephropathy, and new ulcerations, deaths and amputations. Healing rates for various treatment modalities were compared.

The mean follow-up time was 35 months. In the patients with OM, 81% had retinopathy and 38% were nephrotic. In the patients without OM, 50% had retinopathy and 0% were nephrotic. Of all patients, 17% (4/24) had died, and 25% (6/24) underwent amputations. New ulcers developed in 80% (19/24), and 50% of these had an underlying OM.

The original ulcers were treated with antibiotics ($n = 18$, 15 with OM), surgery + antibiotics ($n = 6$, 6 with OM), and local care only ($n = 6$, 1 with OM). Ulcer healing was achieved in 81% (21/26). There were no significant differences in healing for patients with OM treated with surgery + antibiotics (80%) versus antibiotics alone (82%).

We conclude: (1) Clinically unsuspected OM in DU may be a marker for more rapid progression of microvascular disease, (2) DU are associated with a high rate of new ulcerations, amputations, and mortality, and (3) The majority of clinically unsuspected OM in DU may be cured with antibiotics alone.

31. Graves' Thyroid Tissue Transplants in *SCID* Mice: Continued Bias in hTcR V α Gene Family Use. S. De Riu, A. Martin, M. Valentine, L. D. Schultz,* and T. F. Davies. Division of Endocrinology and Metabolism, Mount Sinai School of Medicine, New York, NY, and the Jackson Laboratory,* Bar Harbor, Maine.

We have analyzed the human T-cell receptor (hTcR) V α gene repertoire in thyroid tissue transplants of a patient with hyperthyroid Graves' disease.

Each of 4 blocks of thyroid tissue was transplanted subcutaneously into 12 *scid* mice and 4 weeks later 6 of the mice were injected intraperitoneally with autologous peripheral blood mononuclear cells (PBMC) (10^7 cells per mouse). After a further 3 weeks, mice were sacrificed and total cellular RNA prepared from each of the explants. We used specific oligonucleotides in polymerase chain reactions to amplify 18 different human hTcR V α gene families and the identity of the PCR fragments was confirmed by Southern blot analysis. We then compared the findings in the *scid* explant samples with data obtained with the original thyroid tissue.

Firstly, we found the donor thyroid tissue to express only 8 of the 18 hTcR V α gene families screened (Vα 1–7 and Vα 11). Secondly, a marked bias in hTcR V gene family use was seen in each of the explants. After 7 weeks of transplantation, the explants largely reflected the hTcR V gene repertoire seen in the donor tissue with particularly pronounced expression of Vα 2 and Vα 3 gene families.

Hence, these two V gene families may be involved in the etiopathogenesis of the autoimmune thyroid process in this patient. The transplantation of PBMC into the *scid* mice in this study had no influence on the surviving T cell population within the transplanted thyroid tissue.

Our data underline the value of the *scid* mouse as an in vivo model to study the intrathyroidal lymphocyte population in Graves' disease.

32. Do Gonadotropin-Releasing Hormone (GnRH) Axons Target the Median Eminence (ME) in Vitro? M. C. Rogers, T. J. Wu, A.-J. Silverman, M. J. Gibson. Div. of Endocrinology, Mount Sinai School of Medicine, New York, NY; Dept. of Anatomy & Cell Biology, Columbia University, New York, NY.

GnRH neurons originate in the olfactory placode in mice and migrate into the basal forebrain during embryogenesis. Scattered in the preoptic area (POA) of the hypothalamus, GnRH neurons send axons to the ME and the organosum vasculosum of the lamina terminalis (OVLT) a long stereotyped pathways. POA grafts derived from E15 normal fetuses and placed in the third ventricle of hypogonadal (Hpg) mice lacking a functional GnRH gene demonstrate the ability of GnRH neurons to target the adult host ME with the same precision. Hpg mice with POA grafts respond with increased gonadotropin secretion and gonadal development. Cografts of POA and mediobasal hypothalamus (MBH) containing the ME, suggested that the ME directs GnRH terminal outgrowth. In an organotypic in vitro system we tested this hypothesis.

The E15 embryonic POA was cultivated alone (for control) or in presence of MBH between 1 and 8 days in a polymerized collagen matrix. Direct observation in phase contrast microscopy before sectioning revealed process development as early as 24 h after culture. GnRH cell bodies and processes were detected in POA in 85% of the explants by immunostaining.

GnRH processes were often observed in the collagen matrix facing MBH. The average length of axons was 300 μm but longer axons were noticed. The OVLT sometimes found in the POA dissection seemed to also direct GnRH outgrowth. Numerous growth cones were detected in DiI-treated cultures and GAP 43 immunostaining revealed axons around the POA and MBH after 2 days of culture.

Further characterisation and statistical analysis of the explants as well as co-culture with different parts of the brain will allow us to evaluate any directionality of GnRH outgrowth towards the MBH in vitro.

33. Positive Impact of an Ambulatory Clerkship on the Medical Student's Perception and Interest in Internal Medicine. A. Stagnaro-Green, R. M. Stein. Divisions of Endocrinology and Metabolism and Renal Medicine, The Mount Sinai Hospital, NY.

There has been a progressive decline nationwide in medical student interest in selecting a career in internal medicine. Simultaneously, and independently, there has been an increasing perception that the ambulatory setting should be a major site for the clinical education of medical students. In 1991 the Department of Medicine initiated a 6-week ambulatory clerkship in senior medicine as an alternative to the in-patient subinternship.

Two 2-week blocks were spent with an internist in his/her office and 2 weeks were dedicated to the emergency room. The student was integrated into all aspects of the physician's practice. During the past two years 44 students have participated in the ambulatory clerkship. Extensive questionnaires were completed and debriefing sessions were held.

Ninety-five percent of all the students would recommend the ambulatory clerkship to their colleagues. All students felt that they had adequate patient care responsibility in the E.R., but only 73% responded that patient responsibility in the office was adequate. The last 26 students were asked specific questions concerning the clerkship's impact on their interest in internal medicine. One hundred percent of the students responded that the clerkship improved their impression of the field of internal medicine. Forty-five percent of the students stated that if they had a simular ambulatory clerkship in the third year of medical school it would have impacted on their choice of residencies.

In conclusion, ambulatory education in internal medicine is well received by fourth year medical students and can impact on their choice of residency. An ambulatory experience in internal medicine in the third year of medical school may increase the number of students choosing internal medicine as a career.

34. TSH Independence of Thyroid Follicle Formation in Human Thyroid Organoids Constructed in *SCID* Mice. M. Valentine, A. Martin, P. Unger,† and T. F. Davies. Division of Endocrinology and Metabolism, Department of Medicine and Department of Pathology,† Mount Sinai School of Medicine, New York, NY.

We have shown that the severe combined immunodeficient (*scid*) mouse allows the in vivo reconstitution of thyroid follicles from thyroid monolayer cells when transplanted subcutaneously within an extracellular basement membrane matrix. After 2–3 weeks, these human thyroid "organoids" show an active microfollicular histology and secrete human thyroglobulin into the murine serum in response to recombinant human TSH. Furthermore, such organoids survive for more than 3 months in this functional state. In order to assess whether the follicular reconstitution was TSH dependent we have now examined such organoid construction in T3-induced hyperthyroid *scid* mice where endogenous murine TSH was assumed to be totally suppressed.

By providing water with 12 ug/ml T3 we increased the murine serum T3 levels from a mean of 116 ng/dl in controls to a mean of 2870 ng/dl in T3-fed animals. After 3 weeks, with or without T3-induced hyperthyroidism, thyroid "organoids," derived from normal human thyroid monolayer cells, were transplanted into 6 *scid* mice and allowed to mature for a further 4 weeks.

Histological examination at the time of sacrifice showed similar thyroid follicle formation in both groups indicating that the hyperthyroid state had caused no interference with follicle reconstitution.

These data demonstrate that in vivo thyroid follicle formation may be entirely TSH independent and under the control of local growth factor inducement.

35. Multiple Mechanisms of Regulation of Glucose Transport by Thyroid Hormone in Skeletal Muscle. S. P. Weinstein, E. O'Boyle, R. S. Haber. Division of Endocrinology and Metabolism, Mount Sinai School of Medicine, NY.

The facilitated diffusion of glucose into cells, often the rate-limiting step for cellular glucose utilization, is mediated by a family of glucose transport proteins. In thyrotoxicosis, a state in which increased metabolic rate raises the demand for cellular energy sources, whole-body glucose utilization and insulin-mediated glucose disposal are known to be increased. We have previously shown in skeletal muscle, the main site of insulin-mediated glucose disposal, that the major muscle glucose transporter, GLUT4, is indeed induced by thyroid hormone. Therefore, to test the hypothesis that thyroid hormone increases glucose transport in skeletal muscle, we examined the effect of L-triiodothyronine (T_3) treatment on basal and insulin-stimulated glucose transport and on GLUT4 protein in individual rat skeletal muscles.

Male Sprague-Dawley rats (45–50 g) were treated with or without T_3 in their drinking water (12 mg T_3/L) for 3 days, and $[^3H]$2-deoxyglucose uptake was then measured in the absence or presence of insulin

(10 nM, a maximally effective concentration) in isolated soleus and extensor digitorum longus muscles. GLUT4 protein (per gram tissue) in both muscles was quantitated by immunoblot analysis of detergent extracts.

Data presented below are means ± 1 SE from 3 to 5 experiments.

2-Deoxyglucose Uptake (μmoles/mL intracellular water/30 min)

	Soleus			Extensor digitorum longus		
	$-T_3$	$+T_3$	Change	$-T_3$	$+T_3$	Change
Basal	0.58	1.3	+124%	0.45	1.1	+140%
	± 0.07	± 0.15		± 0.02	± 0.11	
Insulin	4.1	6.6	+62%	2.5	3.5	+42%
	± 0.23	± 0.35		± 0.17	± 0.20	

Concomitantly, T_3 treatment increased GLUT4 protein in soleus by 43 ± 5% and in extensor digitorum longus by 56 ± 10%.

These data directly demonstrate for the first time that thyroid hormone increases insulin-stimulated as well as basal glucose transport in skeletal muscle. Moreover, the fractional increments in insulin-stimulated glucose transport in T_3-treated muscles are similar to the increments in GLUT4 levels, whereas the increments in basal glucose transport greatly exceed the increments in GLUT4. Thus, increased insulin-stimulated glucose transport in T_3-treated skeletal muscle can be accounted for by the induction of GLUT4 protein. However, increased basal glucose transport cannot be fully accounted for by GLUT4 induction alone, and must reflect an additional mechanism, such as increased basal targeting of GLUT4 to active plasma membrane versus inactive intracellular sites.

36. Regulation of the Hepatic GLUT2 Glucose Transporter by Thyroid Hormone. S. P. Weinstein, Elizabeth O'Boyle, Meredith Fisher, R. S. Haber. Division of Endocrinology and Metabolism, Mount Sinai School of Medicine, NY.

Thyroid hormone stimulates both gluconeogenesis and glycogenolysis in the liver, increasing hepatic glucose output. Because the final step in hepatic glucose production is transport across the hepatocyte plasma membrane, we hypothesized that thyroid hormone might also induce the GLUT2 glucose transporter, which mediates glucose influx and efflux in liver.

Rats were rendered hypothyroid or hyperthyroid by treatment for 3 weeks with methimazole or L-thyroxine, respectively, in the drinking water. GLUT2 protein per mg protein in liver was then quantitated by immunoblot analysis of postmitochondrial liver membranes, and GLUT2 RNA per unit DNA was quantitated by Northern analysis.

(% Euthyroid)	Hypo	Euthyroid	Hyper
GLUT2 protein	63 ± 4	100 ± 7	127 ± 9
GLUT2 mRNA	90 ± 7	100 ± 11	132 ± 11

To study more acute effects, hypothyroid rats were treated with T_3, 100 μg/d, for 24 or 96 hours:

(% Hypothyroid)	Hypo	24h-T_3Rx	96h-T_3Rx
GLUT2 protein	100 ± 6	115 ± 11	140 ± 17
GLUT2 mRNA	100 ± 11	253 ± 33	188 ± 21

Thyroid hormone thus induces GLUT2 protein by a pre-translational mechanism in liver, an effect which would facilitate increased glucose efflux. These results indicate that hepatic glucose transport capacity is hormonally regulated.

Gastroenterology

37. Anti-Neutrophil Cytoplasmic Antibody and Refractory Pouchitis: a Case-Control Study. J. Aisenberg, J. Wagreich, J. Shim, T. Heimann, I. Gelernt, P. Rubin, N. Harpaz, L. Mayer, and D. Sachar. Departments of Medicine, Pathology, and Surgery, Mount Sinai Hospital, N.Y. (GCO #92-356-001).

Refractory pouchitis (RP) is a debilitating complication of ileal pouch reservoirs that affects approximately 1% of patients. Although the cause of RP is unknown, it is frequently hypothesized that it reflects underlying Crohn's disease. Since anti-neutrophil cytoplasmic antibody (ANCA) is found in the serum of approximately 70% of patients with ulcerative colitis but only approximately 1% with Crohn's disease, it may help distinguish Crohn's disease from ulcerative colitis.

To test the hypothesis that RP reflects underlying Crohn's disease, we have therefore determined the ANCA status of 26 patients with RP (12 with ileoanal pullthrough pouches (IAPT) and 14 with Kock pouches (KP)) and compared them to 42 matched control subjects without significant pouchitis.

The ANCA was detected in 42% of cases (50% of KP cases and 33% of IAPT cases) and 64% of controls (p = n.s.). Moreover, 3/6 (50%) of IAPT RP subjects who had clinical presentations most suggestive of Crohn's disease tested positive for ANCA. When compared to controls, IAPT cases exhibited significantly more pre-operative extra-intestinal manifestations of inflammatory bowel disease ($p < 0.05$). The presence of pre-operative extra-intestinal manifestations was 100% predictive of post-operative extra-intestinal manifestations ($p > 0.05$).

Review of pouch biopsies from cases of RP revealed no pathognomonic histologic features of Crohn's disease. These data suggest that RP does not reflect underlying Crohn's disease, but may share immunopathogenetic mechanisms with the extra-intestinal manifestations of inflammatory bowel disease.

40. Biliary Oxidized Glutathione in Porcine Hemorrhagic Shock and Reperfusion. A. Manasia, D. Feierman, E. Hannon, Y. Lu, and E. Benjamin. Depts. of Surgery and Anesthesiology, Mount Sinai School of Medicine, New York, NY 10029.

Oxygen-derived free radicals play an important role in the pathophysiology of reperfusion injury. However, assessment of these toxic effects is often circumstantial, owing to the difficulties of quantifying reactive oxygen species. Oxidized glutathione (GSSG) is considered a reliable marker of oxidative stress. We, therefore, chose to measure levels of GSSG in the bile to assess oxygen radical-mediated injury in a porcine model of systemic ischemia/reperfusion.

Methods. Nine adult anesthetized and ventilated pigs underwent laparotomy, cystic duct ligation and hepatic duct cannulation. Hemorrhagic shock (MAP 35–45 mmHg) was maintained for 60 min before shed blood was retransfused. At baseline, end of shock and 30 min post-reperfusion, bile was collected and *N*-ethylmaleimide (NEM) was added to each sample to derivatize reduced glutathione (GSH). Samples were stored at −70°C and assayed for GSSG within 48 hours of collection.

Results. GSSG levels were 2.26 ± 2.17, 0.71 ± 0.46, and 1.60 ± 1.14 μM measured at baseline, shock, and 30 minutes post-reperfusion respectively. Oxygen delivery (DO_2) was 489 ± 105, 119 ± 38, and 498 ± 169 ml/min.

Conclusion. Biliary GSSG levels changed in parallel to systemic oxygen delivery. These data are in agreement with Cummings et al. (BiochemPharmacol 1988:37:967–969), who have demonstrated GSSG oxygen dependence in the perfused rat liver. Although biliary GSSG levels have routinely been used as an indirect assessment of oxygen radical-mediated injury, these findings suggest that biliary GSSG release is O_2-dependent and may not be a specific indicator of oxidative stress.

Hematology

43. A Longitudinal Study of Orthopedic Outcomes for Severe Factor VIII Deficient Hemophiliacs. Louis M. Aledort, M.D. (The Mount Sinai Medical Center, Department of Hematology), Rudy H. Haschemeyer, Ph.D. (The New York Hospital-Cornell Medical Center, Department of Biochemistry), Holger Pettersson, M.D. (University Hospital in Lund, Department of Diagnostic Radiology) and the Orthopedic Outcome Study Group.

Arthropathy is the major cause of morbidity in hemophilia with the majority of treatment on demand. As dosage/bleed vary substantially throughout the world, we investigated the orthopedic outcome of these regimens in an attempt to determine optimal therapeutic approaches.

Twenty-one centers enrolled severe (<1%) Factor VIII deficient hemophiliacs below age of 25 and without Factor VIII inhibitors over a six year period. Physical and x-ray examination scores of ankles, knees and elbows, bleeding episodes, dosage and weeks on prophylaxis were measured. Time lost from work and school as well as days of hospitalization were also monitored.

Physical exam and x-ray scores increased significantly with age, and the number of joint bleeds were significant in determining the Δ score. Approximately 10% of patients entered with all six joints normal. Of these, 50% remained so. The number of bleeding episodes, and year long prophylaxis highly significantly reduced the rate at which joints deteriorate both on physical and x-ray examination. In addition, these patients lost significantly, fewer days from work or school as well as days spent in hospital. Using multivariate analysis the next best dosage regimen is 25–40 u/kg/bleed.

Full-time prophylaxis is very significant for producing the best orthopedic outcome. Response to a bleed with a Factor VIII dose over 25 International Units is probably the next best treatment. The most critical factor for a good orthopedic outcome is the reduction of joint bleeds.

44. Adoptive Immunotherapy of Advanced Metastatic Melanoma Using Ex Vivo Activated Memory T-Cells with and without Cyclophosphamide (CY): Results of a Pilot Study. J. E. Gold, S. D. Ross, and M. E. Osband. Divisions of Hematology and Medical Oncology, Department of Medicine, The Mount Sinai Medical Center, NY; Division of Pediatric Hematology-Oncology, Department of Pediatrics, Boston City Hospital and Boston University School of Medicine, Boston, MA; and Cellcor, Newton, MA.

Autolymphocyte therapy (ALT) is the infusion of autologous peripheral blood lymphocytes (PBL) activated ex vivo by low doses of the mitogenic monoclonal antibody OKT3 and a cytokine-rich supernatant (T3CS) harvested from a previous lymphocyte culture. Ancillary cimetidine is also used at 800 mg po tid to block in vivo suppressor cell activity. The mechanism of action is the enhancement of a recall response by $CD45RO^+$ (memory) T-cells (ALT-cells) to host tumor antigen. The existence of anti-tumor specific T-cells in melanoma patients has been well described, and efforts to utilize them therapeutically have achieved modest tumor response rates. Little long term survival data, however, have been reported.

From 1986–1992, we treated 32 patients with disseminated melanoma using ALT alone (26 patients) or ALT and CY (6 patients). Over this time period, the cell activation method evolved from using cytokine supernatants derived from mixed lymphocyte cultures (MLCS), to using direct OKT3, to the current practice of utilizing OKT3 and autologous cytokines (T3CS). There were 20 males and 12 females, average age 58 years, range 30–82. 18 had failed prior therapies and 14 had no prior therapy. A total of 182 infusions of ALT-cells were given: 18 with cells activated in MLCS, 45 with direct OKT3, and 117 with T3CS.

There were no grade 3 adverse events, and an approximate 20% incidence of grade 1 and 2 reactions to ALT-cell infusions. Survival and tumor responses of 30 evaluable patients are shown:

# Organ systems involved	# Pts	Median survival Observed/expected*	Tumor of Response
3 or more	20	8/2 days	5SD, 1CR (ALT/CY)†
2	9	13/4 days	1CR, 3SD (2 ALT/CY)†
1	1	64/7 days	1CR

* Balch, JCO, 1983.

† SD = <25% increase or decrease intotal tumor burden.

5 of the 7 patients in this category had some lesions decrease and/or completely resolve while other lesions increased in size, but <25%. CR's were noted in (a) a patient with liver, lung, and lymph node metastases, (b) disseminated melanosis of the lower extremity with grossly involved inguinal nodes, and (c) a single liver metastasis.

In conclusion, these data suggest that adoptive immunotherapy using ex vivo activated memory T-cells with and without CY is active with low toxicity, and can result in clinical benefit in patients with disseminated melanoma.

Sponsored by a grant from Cellcor.

45. Adoptively Transferred Ex Vivo Activated Memory T-Cells and Cyclophosphamide: Effective Tumor-Specific Chemoimmunotherapy of Advanced Metastatic Murine Melanoma and Carcinoma. J. E. Gold, D. T. Zachary, and M. E. Osband. Divisions of Hematology and Medical Oncology, Department of Medicine, The Mount Sinai Medical Center, NY; Division of Pediatric Hematology-Oncology, Department of Pediatrics, Boston City Hospital and Boston University School of Medicine, Boston, MA; and Cellcor, Newton, MA.

Autolymphocyte therapy (ALT) is adoptive cellular therapy of neoplastic disease based upon ex vivo activation of autologous peripheral blood lymphocytes (PBL) by either the supernatant derived from a previously prepared one-way mixed lymphocyte culture (MLC), or using low doses of the mitogenic monoclonal antibody OKT3 and a mixture of previously prepared autologous cytokines (T3CS). We have previously demonstrated that non-specific ex vivo activation of splenocytes from murine tumor-bearing hosts (TBH) using an MLC-supernatant (MLCS) or T3CS without the use of tumor antigen, results in the expansion of the $CD44^+$ (memory) T-cell subset. These memory T-cells are the principal component of autolymphocytes (ALT-cells) and mediate in vivo antitumor specificity as demonstrated by decreased primary tumor size, decreased number of lung metastases, and prolonged survival when infused into mice with advanced metastatic neoplastic disease.

To determine if cyclophosphamide (CY) could enhance the effectiveness of these ALT-cells, C57BL/6J TBH with B16 melanoma or Lewis lung (3LL) carcinoma were treated with adoptive chemoimmunotherapy (ACIT) consisting of ALT-cells and varying doses of CY. ALT-cells were derived from the splenocytes of C57BL/6J TBH with B16 melanoma or 3LL carcinoma and activated ex vivo with T3CS. 3LL-TBH and B16-TBH received: 1) ALT-cells derived from either 3LL-TBH splenocytes or B16-TBH splenocytes; 2) CY alone; or 3) ACIT with ALT-cells and CY.

Significantly greater anti-tumor activity as demonstrated by a decreased number of lung metastases (day 21), and cure of primary and metastatic disease (day 100) was seen in B16-TBH and 3LL-TBH that received ACIT using CY with B16-derived and 3LL-derived ALT-cells, respectively, rather than ALT-cells alone, CY alone, or ACIT with CY and reciprocal tumor-derived ALT-cells. TBH cured by ACIT using CY and ALT-cells derived from syngeneic TBH with the identical tumor displayed tumor-specific immunity as they were able to reject a lethal challenge of their previous B16 or 3LL tumor but not reciprocal tumors. TBH cured by ACIT using CY and ALT-cells derived from splenocytes of syngeneic TBH with reciprocal tumors were able to reject lethal challenges of both tumors.

These data demonstrate that effective ACIT using CY combined with ex vivo T3CS-activated $CD44^+$ memory T-cells from TBH conveys long-term tumor-specific immunity.

Sponsored by a grant from Cellcor.

46. Jumping Translocations of Trisomic Long Arms of Chromosome 1 in Acute Myeloid Leukemia (AML). B. Hauschildt, A. Scalise, L. Silverman, A. Gattani, E. Ambinder, V. Najfeld. Tumor Cytogenetics Laboratory, Polly Annenberg Levy Hematology Center and Department of Neoplastic Disease.

Terminal or telomeric associations (TA) of a trisomic chromosome with different intact receptor chromosome in a form of jumping translocations are an unusual phenomena in leukemia. We now report two patients with history of myelodysplastic syndrome who transformed into AML and whose leukemic cells showed trisomy of the long arms (q) of chromosome 1 in jumping translocations with four different receptor chromosomes.

In patient 1, 74 bone marrow metaphases were examined; 70% had the trisomic 1q attached to the short arms of chromosome 22 in the form of der(22)t(1;22)(q12;p13); 17.5% of cells had trisomy 1q translocated onto the short arms of chromosome 15: der(15)t(1;15)(q12;p11) and 4% of cells had TA between trisomy 1q and the end of the short arms of chromosome 8: der(8)t(1;8)(q12;p21). A similar distribution frequency of trisomy 1q in TA with chromosomes 8, 15 and 22 was demonstrated in unstimulated peripheral blood cells: 1%, 14% and 73.5%, respectively.

In patient 2, the major cell population in bone marrow, detected in 49 cells, had a 47,XY,t(4;11)(q10;p15),+11 karyotype. An additional rearrangement consisting of trisomy 1q translocated to the short arms of chromosome 22: der (22)t(1;22)(q12;p13) was detected in 12% of cells. Investigation of chromosomes obtained from unstimulated peripheral blood cultures revealed trisomy 1q in a TA with chromosome 21: der(21)t(1;21)(q12;p13) (33% of cells) as well as with chromosome 22 (33% of cells). Therefore, blood leukemic blasts had trisomy of the long arms of chromosome 1 in jumping translocations with chromosomes 21 and 22.

The mechanisms of jumping translocations and their relationship to the pathogenesis of AML remains speculative because this phenomena has rarely been documented. Based on the hypothesis that loss of telomeric DNA repeats, beyond the critical point, may result in chromosomal instability and cell senescence, jumping translocations in leukemic blasts may be explained by the rapid decrease of telomere length with each cell division. Consequently, some chromosomes may achieve this critical level in a shorter time. We, therefore, performed fluorescence in situ hybridization experiments using telomeric terminal repeat DNA probe. Preliminary results indicated a decrease of telomere repeats on chromosomes involved in these translocations. Jumping translocations were detected just before each patient died and it is conceivable that these translocations are the result of telomere loss and may represent markers for cell death.

47. Cardiotoxicity of Adriamycin in Multidrug Resistant Transgenic Mice. Luis Isola,* Steven Frank,* Pablo Cagnoni,* Jon Gordon.† *Division of Hematology, Department of Medicine, †Department of OBS/GYN and Reproductive Science, Mount Sinai Medical School, NY, NY.

Adriamycin (ADR) is one of the most widely used drugs in the treatment of hematologic malignancies. With the use of colony stimulating factors and bone marrow rescue the severe myelosuppression associated with this agent can be substantially alleviated. However, cardiotoxicity is still a dose limiting toxicity. This limits the use of anthracyclins in salvage and bone marrow transplant preparative regimens. A general strategy proposed to enhance the safety margin of chemotherapy and allow further dose escalation in the transfer of drug resistance genes into cells that are target for toxicity. Among these sequences, the multiple drug resistance (MDR) gene encoding the P-glycoprotein, has been introduced into cells to confer ADR resistance. Transgenic mice (TM) have been previously used by us and others to investigate the potential of genetic engineering of bone marrow resistance *in vivo*.

We have produced three lines of TM with a Herpes virus thymidine kinase (TK) promoter-MDR cDNA construct. Using this model we conducted a pilot study in which we took four animals, 2 TM and 2 controls, through two weekly cycles of intraperitoneal ADR at a dose of 8.5 mg/kg.

In this first study the two TM survived and the controls died one week after the last injection (difference NS). A larger study included 11 TM and 12 controls which received four cycles of ADR at the same dose, the survival for the TM was 36% (4/11) and for the controls 42% (5/12) (difference NS). There was also no significant difference in blood counts between surviving animals in the two groups at the end of the study. The examination of the hearts by optical microscopy showed that the controls had more severe effects of ADR toxicity (myocyte vacuolization and sarcotubular dilatation).

We conclude that: 1) In spite of its ability to elicit high levels of transcription of other genes in TM, TK is not an efficient promoter to drive MDR expression in bone marrow precursors, 2) While TM carrying TK-MDR constructs are not a good model for *in vivo* genetic engineering of bone marrow resistance, they may be useful to investigate the use of MDR genes in overcoming ADR cardiotoxicity, 3) With an appropriate method of gene delivery, MDR may be used to protect the myocardium from ADR toxicity so as to facilitate dose escalation in regimens containing ADR or in patients who have reached the maximum cumulative dose currently recommended. A study with a larger number of mice, P-glycoprotein assays and electron microscopic assessment of ADR myocardial toxicity is ongoing.

48. High Purity vs Intermediate Purity Factor VIII in HIV+ Hemophiliacs: Conclusions of a Prospective 3-Year Study. S. Seremetis, LM Aledort, TS Lau, H Sacks and the Monoclonal Study Group. The Department of Medicine, Divisions of Hematology and Infectious Diseases, and Department of Biomathematics at the Mount Sinai School of Medicine, New York, NY.

Low CD4 lymphocyte counts are associated with increased risk of progression to AIDS in HIV infected persons. In order to test the hypothesis that the use of high-purity products in HIV+ hemophiliacs would result in a difference in the rate of deterioration of immune function, we designed a protocol for a multicenter, prospective, controlled study of asymptomatic HIV infected subjects with hemophilia A who were randomly assigned to receive either an intermediate purity or monoclonal antibody-purified product.

At study entry, all subjects had CD4 counts ≤600 and ≥100, were negative for HBsAg, and had not received any antiretroviral or immuno-modulating drugs. 60 subjects were recruited and 30 subjects were assigned to each group. Subjects were permitted to receive antiretroviral therapy during the study. 35 subjects completed the three-year study, 20 in the monoclonal arm and 15 in the intermediate purity arm.

There were no differences between the two groups in the occurrence of AIDS-defining diagnoses (1 patient in each group). There were however significant differences between the two groups in terms of changes in absolute CD4 counts.

Time	Intermediate	Monoclonal	p
	(Mean ± SD)		
0	378.3 ± 126.5	416.3 ± 139.7	0.4130
12 mo.	337.1 ± 116.8	400.3 ± 161.5	0.2088
24 mo.	268.1 ± 126.8	445.9 ± 191.1	0.0037
36 mo.	190.1 ± 114.7	393.3 ± 200.3	0.0007

The group receiving monoclonal antibody-purified concentrates had essentially stable CD4 counts while a significant drop in CD4 counts was observed in the group receiving intermediate purity concentrates. These differences were independent of the use of antiretroviral therapy.

These data, from the largest and longest such study reported, indicate that the use of monoclonal-antibody purified concentrates is associated with better preservation of CD4 lymphocytes in asymptomatic HIV+ patients with hemophilia A. We also conclude that repeated exposure to some component of intermediate purity Factor VIII concentrates represents a cofactor in the progression of HIV disease in patients with hemophilia A.

49. Nasal Spray Desmopressin (DDAVP) Experience in Home Care and Surgical Prophylaxis. S. V. Seremetis and L. M. Aledort. Division of Hematology, Department of Medicine, Mount Sinai School of Medicine, New York, NY.

The use of plasma products to treat patients with von Willebrand Disease (vWD) and hemophilia has led to transfusion transmitted diseases. The introduction of DDAVP to the U.S. in 1983 has obviated the need for plasma for many of these patients. Currently, DDAVP is administered by intravenous (IV) and subcutaneous (SC) routes. We have previously reported that intranasal (IN) administration of DDAVP via a simple atomizer has produced a bioavailability equivalent to an IV dose of 0.2 ug/ml. In both mild hemophiliacs and vWd patients, this resulted in elevations in FVIII:C, vWF, and vWAg that were comparable to the results of IV administration. Patients whose baseline testing showed favorable results were given the nasal spray for home-care use for bleeding episodes and prior to minor surgical procedures.

We now have efficacy data from 184 such episodes in 18 patients, 13 with vWD, 3 mild hemophiliacs and 2 hemophilia carriers; patients self-scored responses to treatment with IN-DDAVP. 10 women with vWd treated a total of 101 episodes of menorrhagia: 85 episodes were scored as excellent responses, 9 were scored as good, the remaining 7 were scored as minimal. Also in patients with vWd, 54 episodes of joint bleeding, 15 of epistaxis, and one laceration were treated with excellent hemostasis. In addition, one patient underwent extensive dental work and another patient had carpal tunnel release; in both cases patients reported excellent hemostasis. In mild hemophiliacs, 13 episodes of hemarthrosis were treated with IN-DDAVP; all episodes were scored as excellent or good responses. One of the hemophiliacs underwent arthroscopic surgery; hemostasis and healing were judged excellent. Two surgical procedures were performed in hemophilia carriers; both episodes were scored as excellent hemostasis.

We conclude that IN-DDAVP is an efficacious, simple, convenient method for the treatment of mild hemophilia and vWD. It is adaptable for home use and will be a useful addition to the treatment armamentarium for these hereditary coagulopathies.

50. Endothelial Cell Transglutaminase at the Interface of Thrombosis and Fibrinolysis. X. Zhang, W. Borth, P. C. Harpel. Division of Hematology, Mount Sinai School of Medicine, N.Y.

There is increasing evidence that cellular transglutaminases (TGases) play a significant role in cellular adhesion and apoptosis (programmed cell death). TGases are a family of Ca-dependent enzymes which cross-link some protein substrates. Endothelial TGase is thought to play a role in atherogenesis that remains to be defined. We have recently proposed that endothelial TGase functions at the interface of thrombosis, fibrinolysis and tissue modeling by modifying some proteins that have critical functions in thrombosis and fibrinolysis. Modification of these proteins by TGase either creates a prothombotic or fibrinolytic milieu. We have recently shown that apolipoprotein (a) (apo(a)), a unique protein moiety of the atherogenic lipoprotein particle lipoprotein (a) (Lp(a)) is a substrate for TGases. This suggested to us that Lp(a) may be immobilized in the vessel wall upon cross-linking to connective tissue matrix components. Apo(a) is extensively homologous to plasminogen and both are members of a family called kringle proteins which evolved from an ancestral serine proteinase.

Using probes that identify TGase-reactive glutamines and lysines we observed that plasminogen is an excellent TGase substrate. Plasminogen could also be cross-linked to fibronectin, a well characterized adhesion protein and TGase substrate. Human umbilical vein endothelial cells (HUVECs) are a source of TGase in vitro. If HUVECs were incubated with radiolabeled plasminogen, large molecular weight aggregates formed that resisted to reduction and SDS treatment.

These aggregates remained cell associated and no cross-linking of plasminogen was seen in the culture supernatants suggesting that cell surface associated TGase cross-linked plasminogen to cell membrane associated proteins. It is possible that plasminogen becomes cross-linked to pericellular connective tissue matrix components including fibronectin and proteoglycans. On the other hand, plasminogen might become cross-linked to a cell membrane protein or "receptor." HUVEC membranes were prepared by sequential ultracentrifugation steps. The possibility was addressed whether these membrane preparations contained proteins that showed substrate characteristics for TGase. When probed for reactive glutamines we found one protein, p 55, that was highly susceptible for TGase. When probed for reactive lysines we observed one protein that preferentially labeled at a molecular weight of 93 kD.

Our observations indicate that plasma proteins that participate in thrombogenic (i.e., Lp(a)) or fibrinolytic (i.e., plasminogen) processes are modifyed by TGases. Endothelial cells which are binding sites for these proteins express also TGase substrates on their cell surface. It is conceivable that TGase catalyse a tight interaction of these hemostatic factors thereby affecting the biological characteristics of these proteins.

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51. Epithelial Cell Invasion by *Mycobacterium avium* Complex (MAC). S. T. Brown,[1] R. Richardson,[2] and L. W. Riley.[2] Infectious Disease Section, Bronx VAMC & Mount Sinai School of Medicine[1]; and Department of International Medicine, Cornell University Medical College.[2]

The gastrointestinal tract is the most likely portal of entry leading to infection with *Mycobacterium avium* complex (MAC) in patients with AIDS. We examined the interaction between well-characterized clinical isolates of MAC and HeLa cells, a culture line having epithelial cell characteristics.

Isolates of MAC from AIDS and non-AIDS patients were incubated for 48–72 hours at a ratio of 100:1 with HeLa cells.

After thorough rinsing, Kinyoun stains of methanol-fixed cultures showed large numbers of acid-fast bacilli (AFB) associated with HeLa cells from some strains of MAC while the interaction with other strains was negligible. Acid-fastness of HeLa cell-associated MAC from some strains was lost after methanol fixation but present with glutaraldehyde fixation. Electron microscopy of HeLa cell-associated mycobacteria showed that they were intracellular and were surrounded by an electron-transparent zone characteristic of pathogenic mycobacteria.

These findings suggest that there are strain-dependent differences in the ability of MAC to invade HeLa cells. The cultivation of MAC with HeLa cells may be a useful model in which to study virulence factors for MAC.

52. Complications of Adjuvant Steroid Therapy for Presumed *Pneumocystis carinii* Pneumonia (PCP) in an Inner-City Population. T. Cheung,* F. Wallach, S. Cohen, and H. Sacks. Mount Sinai Medical Center, New York, N.Y.

Objective. To evaluate the short- and long-term complications of adjuvant steroid therapy for HIV-infected persons admitted with a diagnosis of presumed PCP.

Methods. Retrospective chart review of all HIV-infected persons admitted with a diagnosis of presumed PCP and on adjuvant steroid therapy from June to December 1992.

Results. Twenty-one patients have been treated by this method. Racial groups included 10 Blacks and 11 Hispanics. Their ages ranged from 25 to 62 (mean 36.1). Their risk groups were: 15 intravenous drug users (IVDU), 4 heterosexual and two with both IVDU and heterosexual risk factors. Mean CD4 count was $28.4 \pm 0.6/\text{mm}^3$. PCP therapy included: 17 received trimethoprim-sulfa and 4 pentamidine; one was given a subsequent course of primaquine and clindamycin. Average steroid use was 563.5 mg of prednisone equivalent. Short-term complications (<1 month) included glucose intolerance in 2, psychosis in 1, fulminant tuberculosis in 2, disseminated *Mycobacterium avium* complex in 2. Long-term complications: *Cytomegalovirus* retinitis in 2 (one with disseminated CMV disease of multiple organs). Two patients died during therapy. One died two months later of end-stage HIV disease; two patients were lost to follow-up and the rest were still alive.

Conclusion. Adjuvant steroid therapy for presumed PCP is generally safe and effective. However, in areas of high tuberculosis incidence, the safety of adjuvant steroid therapy may need to be reevaluated. Diagnostic procedures should be performed to rule out other possible infections.

53. Prevalence of Latex Glove Allergy in a Population of Health Care Workers (Operating Room Labor and Delivery Nurses and Phlebotomy Workers) at Elmhurst Hospital Center: 1993. Salim Gopalani. Department of Medicine. Elmhurst Hospital Center.

Latex glove allergy is increasingly recognized as a cause of occupational morbidity especially among health care workers, who have increased latex exposure in recent years. A study was conducted to assess the prevalence of latex glove allergy in operating room, emergency room, labor and delivery nurses and phlebotomy workers at Elmhurst Hospital Center.

A questionnaire was distributed to 114 health care workers to identify those individuals who had symptoms of allergy to latex gloves and also to characterize associated factors such as length of employment, duration and frequency of use.

The response rate to the survey was 63.1% (n = 72) there were 21 (29.1%) responses indicating latex glove allergy; there were 0% reported allergy to nonoccupational exposure to latex. Seven workers (9.7%) reported access to non-latex gloves was inadequate.

The prevalence to allergy may be lower, as workers with allergic symptoms reported promptly as compared to workers (non-responder) with no symptoms. Latex allergy, as ascertained by self-report in this study, appears to have substantial prevalence in these workers, and non-latex gloves should be readily available for workers allergic to latex.

54. Essential Hypertension in Caribbean Hispanics: Sodium, Renin, and Effects of Therapy. C. Laffer and F. Elijovich. Division of General Internal Medicine, Mount Sinai School of Medicine, New York, NY.

Seventy-one Hispanic hypertensives of Caribbean descent (77% Puerto Rican, 80% female) participated in 116 treatment trials. Age was 57 ± 1 yrs (29–79); diabetes and obesity were present in 27% and 70%, respectively.

After 3–4 weeks off therapy, UNaV was 143 ± 11 mEq/d (34–445, n = 66) and exceeded 100 in 64%. PRA was 0.9 ± 0.1 ngAI/mL/hr (0–3.4, n = 84) and was below the reported lower 95% confidence limit for PRA/UnaV of normotensives in 64%. PRA correlated with UNaV ($r = -0.36$, $p < 0.01$) but not with age. Double-blind therapy (8–12 wks) was not given if diastolic BP was <90 mmHg (n = 11) or >110 (n = 10) at the end of the washout phase. Randomization to placebo (n = 14) reduced BP by $-6 \pm 4/-7 \pm 2$.

Significantly greater reductions in BP were observed with hydrochlorothiazide (H, $-23 \pm 2/-11 \pm 1$, n = 16) and its combinations with converting enzyme inhibitors (H-ACE, $-23 \pm 3/-14 \pm 2$, n = 13) and β blockers (H-β, $-30 \pm 4/-17 \pm 2$, n = 14). H-β was given in random sequential fashion, permitting calculation that 67% of the BP fall was due to H. In contrast to the antihypertensive effects of diuretic-containing regimens, those of monotherapy with ACE ($-3 \pm 4/-5 \pm 2$, n = 25) or β ($-8 \pm 5/-8 \pm 2$, n = 13) were not different from placebo, despite reduction in heart rate with β (-15 ± 2 bpm, $p < 0.001$). The reduction in BP by H correlated with PRA ($r = -0.45$, $p < 0.05$) and was associated with weight loss (-2 ± 1 lbs, $p < 0.01$). Treatment with H, ACE and H-ACE increased PRA by 0.4 ± 0.2, 0.6 ± 0.2 and 1.8 ± 0.7, respectively ($p < 0.05$ for each).

We conclude that Hispanic hypertensives are obese with low, but stimulatable, PRA and high UNaV. We speculate that high sodium intake is a cultural carry-over of ancestral adaptation to tropical climates in Caribbean Hispanics, and that it explains their previously unreported pattern of response to antihypertensive therapy.

55. Impact of Expanded Tuberculosis (TB) Isolation Policy on a New York City Urban Teaching Hospital. M. H. Mendelson,* A. Moore, M. Vigo, L. Finkelstein, B. R. Meyers, J. Dong, J. Solomon, and S. Z. Hirschman. The Mount Sinai Medical Center (MSMC) New York, New York.*

Due to the recent epidemic of TB, atypical presentations of TB and reports of nosocomial transmission, hospitals have implemented expanded indications for TB isolation. At the MSMC these have included clinical/radiographic respiratory processes in all HIV positive/high risk patients in addition to classical TB presentations in all patients.

145 patient admissions (pt adm) (139 pts) from 12/1/92 to 2/16/93 were placed on TB isolation. 30 pt adm had a final diagnosis of TB (20.4%), 28.3% bacterial infection, 13.8% pneumocystis pneumonia, 33.8% unknown, 5.5% other.

A comparison of TB vs. non TB pt adm showed: mean age (36, 41 yrs.), HIV positive (46.7%, 55.7%), previous TB history of (h/o) (33.3%, 9.6%; $p < .01$), productive cough (57%, 64%); CXR findings: focal/alveolar infiltrate(s) (67%, 50%), cavitation (33%, 10%; $p < .01$), increased interstitial markings/infiltrates (3%, 27%; $p < .01$), upper lobe finding (17%, 14%), adenopathy (23%, 13%), negative (10%, 12%); and mean isolation days (26, 10). 30% TB pt adm. were AFB smear—negative.

Although there was a significantly greater incidence of h/o TB and cavitation and lower incidence of increased interstitial markings/infiltrates in TB pts, clinical/radiographic parameters are not clearly defining in either group. Therefore, isolation of non-TB patients will occur for significant periods as a component of a TB control program.

56. Multivariate Analysis of Needlestick/Sharps Injuries (SIs) in 10 New York State (NYS) Hospitals, 1991. M. H. Mendelson,* L. Short, J. Godbold, C. Schechter, X. Wu, B. R. Meyers, S. Z. Hirschman, L. Chiarello. Mount Sinai School of Medicine, New York, NY and the New York State Department of Health.

To target priorities for injury-reducing devices and strategies, an analysis of 1095 reported SIs from 10 NYS hospitals in 1991 was conducted.

58.7% SIs involved RNs, 16.4% MDs, 5.4% housekeeping/maintenance, 3.5% laboratory workers. Hollow bore needles (N) accounted for 75.4% (N/syringe 32%, N/IV tubing (IVT) 15%, butterfly N 8.5%, unattached N 5.3%, vacutainer N 4.5%, IV stylet 3.9%); sutures 7.1%, lancets 5.0%, scalpel blades 4.8% and glass 2.4%. Associated procedures included: IV delivery related (IVDR) 18.3%, phlebotomy (PHL) 11.7%, IM/SQ/ID injection 11.4%, finger/heelstick 5.7%, IV insertion 5.3%. Distribution of PHL SIs by sharp type: butterfly N 42.5%, vacutainer N 30%, N/syringe 25.8%. 40.2% SIs occurred during the procedure, 41% after use (5.8% recapping) and 17% during/after disposal.

Log-linear analysis showed the distribution of sharp types for MDs (55% hypodermic (hypo) N, 25.8% butterfly N) to differ from that for RNs (45% hypo N, 23% N/IVT) ($p < .01$). IVDR SIs occurred less frequently in hospitals with vs. without safer systems: 1.47% vs. 12.53% (hep lock); 4.48% vs. 8.04% (IVPB) ($p < .05$).

Devices with passive safety mechanisms should reduce SIs by 48–67%, and active mechanisms by 17–28%. A significant impact on worker safety and prevention of transmission of blood-borne pathogens should follow.

57. Antituberculous Agents Causing Acute Hepatic Failure: Successful Treatment with Orthotopic Liver Transplantation (OLT). BR Meyers, M Halpern, C Miller, M Schwartz, P Sheiner, MH Mendelson. Divisions of Infectious Diseases & Transplantation, Mount Sinai Hospital, N.Y.

Use of antituberculous agents for prophylaxis and treatment of sensitive and resistant tuberculosis is increasing.

We report 7 patients with acute hepatic failure after receiving tuberculosis prophylaxis (6) and treatment (1) in 1991 and 1992. There were 2 males (1 Black, 1 Oriental) and 5 females (4 Hispanics, 1 Black), mean age 41.2 years (5–69).

Possible cofactors for liver toxicity were found in 5:4 (medicines), 1 (ethanol), 1 (hepatitis B Virus), 1 (Epstein-Barr virus). Isoniazid (INH) was given for 6–25.5 weeks (mean 12.8) ($n = 6$) and pyrazinamide (PZA) for 3 weeks ($n = 1$) before presentation. Encephalopathy developed 1–57 days (mean 16.7) after stopping antituberculous agents. Toxicity at presentation/and prior to OLT were: prothrombin time 25.5/34.1 (Secs), bilirubin 16.6/33.9 (mg/dL), AST 2101/397 (IU/L), ALT 2028/788 (IU/L). Pathology revealed massive hepatic necrosis. Patients received OLT 11–61 days (mean 29.4) after presentation. Awaiting OLT, 1 died of hemorrhage and infection. Survival: 4/5 OLT recipients (mean 418.7 days, range 126–759 days), 3/4 patients with INH toxicity; 1 patient with sequential INH and PZA for multiple drug resistant tuberculosis prophylaxis survived following 3 OLTs (2 ABO incompatible livers).

Conclusions. Since antituberculous-agent-induced acute hepatic failure can develop rapidly once symptoms occur, and survival after OLT was 80%, referral for OLT is indicated early in management. Other cofactors may enhance antituberculous agent toxicity and should be looked for to identify patients at risk of acute hepatic failure.

58. Cytomegalovirus (CMV) Infections in Liver Transplant Patients (pts): Decreased Incidence over 4 Years Associated with High Dose Acyclovir and Intravenous Immunoglobulin (IVIG). BR Meyers, M Halpern, C Miller, M Schwartz, P Sheiner, E Emor, MH Mendelson, L Chodoff. Divisions of Infectious Disease, Liver Transplantation & Department of Pharmacy, Mount Sinai Hospital, N.Y.*

From 9/88–8/90 (A), 98 pts underwent 118 orthotopic liver transplants (OLT); from 9/90–11/92 (B) 301 pts underwent 347 OLT. Prophylaxis for CMV in A was 200 mg oral acyclovir bid to all pts, and 500 mg/kg IV IgG once weekly for 4 wks then qow × 4 to CMV negative recipients (R−) who received CMV donor positive (D+) livers. During B, pts received acyclovir 100 mg IV q12h perioperatively then 800 mg po q6h × 12 wks, plus IVIG to all R− pts. A and B were similar for: mean time of surgery, underlying diseases, drug usage OKT-3 and FK-506, and age (47 yo in A, 43 in B).

In A/B, CMV caused viremia 1/4, hepatitis 19/15, pneumonia 3/3, esophagitis 2/2, gastro/duodenal colitis 3/2 and retinitis 0/1. CMV disease developed more frequently in A 25/103 (24%) than B 22/289 (7.6%) ($p = 0.01$), and in all sub-groups of A and B examined:

	A (%)	B (%)	*p*
D+/R+	8/34 (23.5)	12/125 (9.6)	0.05
D+/R−	8/13 (61.5)	8/46 (17.4)	<0.001
D−/R+	7/33 (21.2)	8/85 (9.4)	NS
D−/R−	6/26 (23.1)	1/33 (2.9)	<0.025

There was a trend to develop CMV earlier in A than B (51 vs 92 days; $p = 0.058$). In both time periods (A + B), 35/276 (12.6%) of recipient positive (R+) and 23/119 (19.3%) of recipient negative (R−) developed CMV ($p =$ NS). For all R+ there was no association between donor status and development of CMV; 20/159 (12.5%) D+ and 15/119 (12.6%), D− ($p =$ NS). For all R− there are more cases of CMV among D+ than D−; 16/59 (27%) D+ and 7/60 (11.6%) D− ($p \leq .05$). Rejections during A 86/124 (69%) and B 227/326 (70%) were similar ($p =$ NS). In A, CMV disease occurred in pts rejecting 17/64 (26%) and nonrejecting (8/39) (20.5%) ($p =$ NS). In B, CMV disease occurred in pts rejecting 17/155 (11%) versus 5/134 (4%) without rejection ($p \leq .05$).

Conclusions. CMV infections were decreased in B versus A. CMV prevention does not appear to reduce the incidence of rejection; with rejection, CMV disease is less frequent when CMV prophylaxis is more effective. CMV donor status was associated with increased infection only in the negative recipient who received a positive organ. High dose acyclovir was associated with less CMV disease in all recipient-positive patients receiving donor positive liver. High dose acyclovir plus IVIG was associated with less CMV disease in all recipient negative patients regardless of CMV donor status.

59. Enterococcal Infections in Liver Transplant Patients: Increase in Multiple Resistant Strains of *E. faecium*. BR Meyers, M Halpern, MH Mendelson, C Miller, L Chodoff. The Divisions of Infectious Diseases, Liver Transplantation & Pharmacy, Mount Sinai Hospital, N.Y.

From August 1988 to 1990 (A), 98 patients underwent 118 orthotopic liver transplants and from September 1990 to 1992 (B), 301 patients had 347 orthotopic liver transplants. Antibacterial prophylaxis for A consisted of parenteral ampicillin (2 g) q6h or vancomycin (1 g) qd (20%), and cefotaxime (1 g) q8h × 72 hours. Selective bowel decontamination began in B with oral gentamicin, nystatin and polymixin, given qid, and as oral paste. Parenteral antibiotics in B were cefotaxime plus vancomycin. The mean age, time of surgery, number of rejections and underlying diseases were similar for A and B.

From August 1988 to September 1992 the rate of enterococcal infections including *E. faecalis* and *E. faecium* for liver transplants varied between 7.1 and 48%. The rate of all enterococcal infections/transplants were: 28% (A) and 26% (B), (p = NS). For A/B: 13%/14% of all transplants (tx) had *E.Fm* isolated. Within B however there was increase in *E. faecium* (*E.Fm*) isolates between Aug 90–Dec 91, 18/197 tx (9.1%) and Jan–Dec 92, 39/157 tx (24.8%). During A/B: *E.Fm* (12%)/(24%) isolates came from blood, (12%)/(9%) wound, (6%)/(7%) bile, and (3%)/(9%) from peritoneum. During A/B, resistance of these isolates were: (33%)/(84%) to ampicillin, (0%)/(49%) to vancomycin, (33%)/(71%) to synergy screens with ampicillin plus streptomycin, and (33%)/(59%) to ampicillin plus gentamicin. There were (0%)/(36%) that were resistant to all above antibiotics.

Conclusions. The incidence of all enterococcal infections in A and B were similar (p = NS). In B vs A: there were more *E.Fm* isolates resistant to ampicillin (p = less than .01), vancomycin (p = less than .001), and ampicillin/streptomycin (p = .01). Resistance to all antibiotics tested increased strikingly in 1992 with 79.5% of *E.Fm.* resistant to all agents tested. Selective bowel decontamination may be associated with the isolation of multiple resistant strains of *E.Fm.* Both blood isolates of *E.Fm* and antibiotic resistance to these strains are increasing; newer antimicrobial strategies will be necessary to treat these serious infections. Doxycycline has proven efficacious in many of these cases.

60. **The Management of Persons Exposed to Multidrug-Resistant Tuberculosis; A Decision Analysis.** David N. Rose, M.D. Divisions of General Medicine and Infectious Diseases and Department of Community Medicine.

Purpose. To analyze various antituberculosis drug regimens to be used as preventive therapy for persons exposed to multidrug-resistant (MDR) tuberculosis (TB).

Methods. A decision analysis was performed for immunocompetent and immunodeficient patients with 12 types of exposure to MDRTB (various probabilities of infection with organisms of various sensitivities to antituberculosis drugs). Antituberculosis drugs were categorized as first-line [isoniazid (INH), rifampin (RIF)], second-line (pyrazinamide, ethambutol, streptomycin, quinolones) and third-line drugs (others); 13 drug combinations were studied. Second-line drugs were assumed to be less effective and more toxic than INH, and third-line drugs more so. A Markov model was used to compare the number of deaths over 10 years among 30-year old people with and without each regimen. 1400 combinations of patient type, exposure type, regimen, and assumptions [favorable, skeptical, and mid-range (base case)] were studied.

Results. Recent tuberculin converters will have greatly reduced mortality from preventive therapy under most circumstances. For example, immunocompetent persons with 0.5 probability of infection with drug-sensitive TB and 0.5 probability with MDRTB (resistant to INH and RIF but sensitive to second-line drugs) have 50% less mortality with a regimen of INH and a second-line drug (than without preventive therapy) and 44% less mortality with a second-line drug alone, under base case assumptions. These regimens are effective even under a combination of the most skeptical assumptions regarding drug effectiveness and toxicity. In certain circumstances, such as exposures to organisms resistant to second-line drugs, and under the most skeptical assumptions, the optimal strategy is no preventive therapy. Immunodeficient persons have even more benefit from various regimens, and fewer circumstances when no preventive therapy is best. This is true even if these persons are anergic, and the probability of recent infection is only 0.5. When there is even a low probability of exposure to INH-sensitive organisms (0.25 probability or higher), the best strategy is preventive therapy with INH plus second-line or third-line drugs.

Conclusions. Preventive therapy benefits most persons exposed to MDRTB. The optimal strategy depends upon best estimates of the drug sensitivity of the organism(s). Even under very skeptical assumptions regarding preventive therapy, certain regimens are beneficial for many exposures.

61. **The Tuberculin Skin Test and Isoniazid Preventive Therapy.** David N. Rose, M.D., Clyde B. Schechter, M.D., Jack J. Adler, M.D. Divisions of General Medicine, Infectious Diseases and Pulmonary Medicine and Critical Care, Department of Medicine and the Department of Community Medicine.

Background. The tuberculin skin test is the only diagnostic test for latent *Mycobacterium tuberculosis* infection. Latent infection can activate at any time, but isoniazid preventive therapy can prevent activation. The tuberculin test's inability to accurately identify *M. tuberculosis* infection and isoniazid hepatotoxicity complicate the decision to prescribe isoniazid.

Purpose. To examine the interpretation of the tuberculin skin test by addressing two questions: (1) what is the probability of *M. tuberculosis* infection at each tuberculin reaction size, and (2) for which tuberculin reactors do the benefits of isoniazid outweigh the risks?

Design. We modeled the probability of infection as a function of tuberculin reactivity size, the prevalence of nontuberculous mycobacterial infection, and the presence or absence of risk factors for recent or remote infection. The preventive therapy decision depends on these and other variables. We analyzed the same studies referenced by the Centers for Disease Control's advisory committees in their recommendations. We also surveyed advisory committee members about uncertain variables and then conducted a decision analysis.

Results. The probability of *M. tuberculosis* infection varies from 0.01 for people from southern states with 2 to 4 mm tuberculin reactions to 1.0 for all persons with reactions of 15 mm or more. The benefits of 24 weeks of isoniazid preventive therapy outweigh the risks for: all persons 5 to 65 years old with $\geqslant$10 mm reactions, except some persons with nonhematologic neoplasms; most persons with 5 to 9 mm reactions who have clinical or social factors that raise the tuberculosis risk and some with no additional risk factor; and some persons with 2 to 4 mm reactions, especially those with HIV infection, fibrotic lesions on chest x-ray, or recent close contact with active cases. The benefits are greater with 52 weeks of preventive therapy.

Conclusions. Tuberculin reactivity only indicates a probability of *M. tuberculosis* infection. Current standards for labeling reactions as "positive" misclassify many reactors, and these classifications should be avoided. Twenty-four or 52 weeks of isoniazid preventive therapy would benefit many people not covered by current recommendations.

62. **Tuberculosis Sensitivity Patterns, Predictors of Multidrug Resistance, and Implications for Initial Therapeutic Regimens at a New York City Hospital.** David N. Rose, André C. Weltman. Divisions of General Medicine and Infectious Diseases and Department of Community Medicine.

Objective. To identify predictors of multidrug resistant (MDR) tuberculosis (TB); and to analyze the potential effectiveness of the standard initial 4-drug regimen and other regimens.

Design. A case-control study of all tuberculosis patients at Mount Sinai Hospital in 1991 and 1992, and a descriptive analysis of the isolates' susceptibility patterns to determine potential effectiveness of initial drug regimens. A potentially effective regimen is assumed to have at least two drugs active against an isolate. MDR-TB is defined as resistance to isoniazid (INH) and rifampin (RIF).

Results. Isolates from 172 patients were studied; 28.5% were resistant to INH, 21.1% to RIF, 15.9% to ethambutol (EMB), 11.3% to pyrazinamide (PZA), 18.6% to streptomycin, 13.1% to ethionamide (ETH), 2.4% to cycloserine (CS), and none to capreomycin (CAP) or ciprofloxacin (CIP). Thirty-two (18.6%) isolates were resistant to both INH and RIF. AIDS, HIV seropositivity, female gender, residence in the Bronx, and race were significantly associated with MDR-TB. The 4-drug regimen of INH, RIF, PZA, and EMB is potentially effective for 81% to 85% of all patients. The subgroup of patients with the most benefit from this combination is patients without AIDS, from 88% to 89% potential effectiveness. The subgroup with the least benefit is patients with AIDS and prior TB therapy, from 60% to 80% potential effectiveness. The substitution of ETH, CIP, CAP, or CS for EMB improves potential effectiveness moderately. Most 5-drug regimens do not have substantially higher potential effectiveness than 4-drug regimens. Only 5- or 6-drug regimens containing two or three of CAP, CIP, CS, and ETH offer substantially higher potential effectiveness.

Conclusions. We found high levels of MDR among the TB patients at our hospital. MDR-TB in these patients is associated with HIV infection, AIDS, female gender, residence in the Bronx, and certain racial groups. The 4-drug initial regimen used in New York City is inadequate for our patients. Only certain 5- or 6-drug regimens have the potential for substantial effectiveness as initial therapy.

63. **Screening for HIV Risk Factors and Referral for HIV Testing in the Medical Primary Care Clinic at Elmhurst Hospital Center, 1993.** A. D. Urena, M.D.

Primary care physicians are in a unique position to screen and educate patients at risk for HIV infection. A study was conducted to evaluate screening and referral practices of physicians in the Medical Primary Care Clinic (MPCC). MPCC is a public based clinic providing comprehensive primary care services with 28,000 visits a year by 9,000 patients.

A random sample of 73 charts was selected. In 40 charts (55%) the standard history form included questions on HIV risk factors; of these, 39 charts (98%) contained documentation of risk factor historical information; one (3%) did not. Five patients (13%) were identified as being at risk for HIV infection. Three (60%) had been recently tested; of the two not tested (40%), documentation of referral for testing was noted in the chart for one patient (50%) and no documentation of discussion or referral was found for the other patient (50%). In 33 (45%) of the total charts reviewed, the initial history was taken prior to 1990 when the standard history form in use did not include printed questions on HIV risk factors. None of these charts contained initial or updated historical information concerning HIV risk factors.

Patients initially evaluated prior to 1990 should have HIV risk factor screening, all patients may benefit from interval updating of risk history. While increased physician and patient awareness since 1990 may have resulted in the 98% rate of screening for HIV risk factors, these results suggest that use of the amended history form may influence physician behavior.

Further study is suggested to evaluate the effectiveness of screening and referral in the MPCC. This is an important clinical issue that is relevant to all physicians especially those working in the primary care setting.

64. Caesarean Section to Reduce Perinatal Transmission of Human Immunodeficiency Virus: A Meta-Analysis. Paolo Villari, MD, Cathie Spino, MD, Thomas C. Chalmers, MD, Joseph Lau, MD, Henry S. Sacks, Ph.D., MD. Harvard School of Public Health, Boston; Facolta' di Medicina e Chirurgia, Universita' degli Studi "G. D'Annuzio," Chieti; New England Medical Center, Boston; Mount Sinai School of Medicine, New York.

Objective. Individual epidemiologic investigations into the association between type of delivery and perinatal HIV transmission have been suggestive but inconclusive. Meta-analysis was used in an attempt to establish if there is, at present, adequate evidence concerning the effectiveness of caesarean section in reducing vertical HIV transmission rates.

Methods. The MEDLINE data retrieval system and other sources were used to identify studies containing data on the relationship between type of delivery and vertical HIV transmission. No randomized control trials were located. Seven of the 11 cohort studies identified were included in the meta-analysis. Crude or, when available, adjusted data were extracted and pooled.

Results. The overall weighted risk of perinatal HIV infection was 21.8% after vaginal and 15.8% after caesarean delivery. This difference was statistically significant. Pooling data of all studies yielded an overall odds ratio of 0.66 (95% Cl: 0.48, 0.91) (Random effects model; DerSimonian and Laird method). Approximately 16 (95% Cl: 43, 10) HIV-infected women must deliver by caesarean in order to prevent 1 case of HIV perinatal infection.

Conclusions. Results of this study show that performing elective caesarean section in HIV-infected women is potentially a very effective procedure. However, the non-experimental nature of the individual studies leads us to conclude that randomized control trials are indicated before setting specific guidelines for mode of delivery in HIV-infected women.

Geriatrics

65. 25-Hydroxyvitamin D in Elderly Nursing Home and Enriched Housing Residents in New York City. C. Feiner, M. Mulvihill, B. Taylor, W. Bauman, H. Smith, E. Weintraub, P. Tsitouras. Dept. of Geriatrics, The Mount Sinai School of Medicine, New York, NY, Jewish Home and Hospital for Aged, Bronx, NY, and Bronx VA Medical Center, Bronx, NY.

Although serum 25-hydroxyvitamin D (25-OH) has not been demonstrated to be low in American community dwelling elderly, there is conflicting data concerning levels in institutionalized elderly.

We examined serum 25-OH in 16 female Caucasian nursing home residents exposed to small amounts of sunlight ($\leq$15 min/day for preceding three months) vs. 16 age-matched enriched housing residents exposed to large amounts ($\geq$60 min/day). History of sunlight exposure, diagnoses, medications and functional status were obtained by chart review and interviews. Dietary data were obtained by 3 day videotaped assessment. Fasting blood assays were done in September and October; 25-OH was measured by RIA.

Mean 25-OH level was 20.0 ± 7.4 ng/ml in the high exposure and 18.4 ± 6.5 ng/ml in the low exposure group (p = 0.35, NS). Low 25-OH levels ($\leq$19 ng/ml) were present in 31% of residents with high sunlight exposure and in 56% of residents with low sunlight exposure. Mean vit. D intake was 252 ± 176 IU in the high exposure and 305 ± 226 IU in the low exposure group (P = 0.52, NS). There was a significant correlation (r = 0.45, p = 0.016) between 25-OH and vit. D intake when both sunlight exposure groups were combined. There was no significant correlation between serum calcium (r = 0.13, p = 0.48) and serum phosphorus (r = 0.20, p = 0.27) versus 25-OH.

We conclude that there is a high prevalence of low 25-OH levels in nursing home and enriched housing residents which, as opposed to sunlight exposure, seems to be a function of vitamin D intake. No metabolic consequence of low 25-OH was detected but data suggest a risk for hypovitaminosis D. Closer attention to vitamin D intake in these populations is indicated.

66. Drug Treatment of Hypertension in the Elderly: A Meta-Analysis. Jorge T. Insua, MD, Henry S. Sacks, PhD, MD, Tai-Shing Lau, PhD, Joseph Lau, MD, Dinah Reitman, MPS, Thomas C. Chalmers, MD. From the Departments of Community Medicine (J.I., H.S.), Geriatrics and Adult Development (J.I.), Medicine, Biomathematical Sciences (H.S., T-S.L, D.R.), Mount Sinai School of Medicine of CUNY, New York, NY: the Technology Assessment Group, Harvard School of Public Health, Boston, MA (T.C.C.), and the Boston Department of Veterans Affairs (J.L.).

Purpose. To examine by meta-analysis the effect of antihypertensive drug treatment on total mortality, cardiovascular mortality, and cause specific morbidity and to analyze the effect of severity of illness and age on outcome, in the elderly population.

Data sources. A literature search for randomized controlled trials of hypertension in the elderly.

Study selection. Randomized control trials of drug treatment of hypertension with endpoints of all cause and/or cardiovascular mortality reported separately for elderly patients.

Data extraction. Mortality and/or morbidity endpoints in patients over 59, were pooled by determination of typical odds ratio. A meta-regression was used to study heterogeneity.

Results. Nine major trials were identified, with a total of 15,559 patients over 59. The ranking of the trials by severity of illness was related to treatment outcome. Death rates varied between 2.7% and 77.2%; stroke and coronary mortality increased with severity of illness rank ($p < 0.0001$). Meta-analysis showed that overall, treated patients had approximately 12% reduction in mortality, (odds ratio (OR) 0.88, 95% confidence interval (CI) 0.80–0.97, 953 vs 1069 events, p = 0.0092). There was 22% reduction in vascular deaths (OR 0.78, 95% CI 0.69–0.89, 462 vs 584, p = 0.00017), 36% for stroke (OR 0.64, 95% CI 0.49–0.82, 94 vs 149, p = 0.0005), and 25% reduction of coronary heart disease mortality (OR 0.75, 95% CI 0.64–.88, 263 vs 350, p = 0.00055). Coronary morbidity was reduced 15% (OR 0.85, 95% CI 0.73–0.99, 325 vs 379, p = 0.036) and stroke morbidity reduced 35% (OR 0.65, 95% CI 0.55–0.76, 247 vs 382, $p < 0.00001$).

Conclusion. Overall, treatment of hypertension in elderly patients produces a significant benefit in total mortality and cardiovascular morbidity and mortality. However, this benefit may be reduced in the more severely ill elderly.

67. Validation of the GDS (YESAVAGE) Depression Screen in the Nursing Home. Shawn McGivney MD, Brian Taylor PhD, and Michael Mulvihill DPH. Jewish Home and Hospital for Aged, New York, and Mount Sinai Medical Center, New York, NY.

The GDS (Geriatric Depression Scale) has demonstrated validity among ambulatory elderly but is less useful in nursing home (NH) populations, probably because of high rates of cognitive impairment. We therefore sought the lowest level of Mini Mental Status Exam (MMSE) score for which the GDS would remain valid.

A total of 66 of 168 newly admitted residents to the NH were able to complete psychiatric assessment, undergo an MMSE and GDS. The psychiatrist and testers (who were virtually all non-MDs) were blinded to each others' results. Using a cut off of 10 or greater on the GDS to indicate depression, the validity of the GDS with the psychiatric diagnosis was made at ever decreasing levels of cognitive function.

In all residents the sensitivity and specificity were 63% and 83%

respectively. When only those with an MMSE of greater than or equal to 15 were included, the corresponding values were 84% and 91%. The proportion of the NH residents screened meeting this cut-point was 64%.

This two step procedure of first selecting those with MMSE greater than or equal to 15 increases the utility of the GDS in NH's and should improve the diagnostic process for the underdetected problem.

68. **Behavioral and Cognitive Changes in Vasopressin-Secreting Transgenic Mice.** Myron Miller, Vahram Haroutunian,* Michelle Wiltshire-Clement,* and Shigeki Kawabata.* Depts. of Geriatrics & Adult Devel., & Psychiatry, The Mount Sinai Med. Ctr., NY, NY.

Vasopressin effects on the central nervous system of rats and mice include enhancement of emotionality, attention and arousal. We have developed a line of transgenic mice which overexpresses the rat gene for vasopressin with resultant increases in vasopressin content in brain and the peripheral circulation.

Locomotor behavior in 8 to 11 months-old male mice homozygous and heterozygous for the rat transgene, as well as normal controls, was evaluated in an open field apparatus for 5 consecutive days and again 9 and 10 days later.

Total distance traveled by the animals during days 1 to 4 declined each day for each group, indicating habituation. The distance travelled on day 4 was significantly lower in homozygous mice (3912 ± 991 cm, SEM) than in heterozygous (6773 ± 552 cm, $p < 0.005$) or normal animals (6859 ± 853 cm, $p < 0.02$). Introduction of a novel object into the center of the field on day 5 resulted in increased center field exploration which was most pronounced in the heterozygous group. Retesting on day 14 demonstrated retention of long-term habituation by all 3 groups, with the homozygous mice showing the greatest effect. Learning and memory capacity was assessed by passive avoidance testing using a light-dark shuttle box. Initial latencies did not differ between the 3 groups. Retesting 72 hrs after foot-shock showed no significant differences among the mice on retention test performance, indicating equal learning and memory for the passive avoidance task. Following an 18-hour period of fluid deprivation, homozygous mice drank significantly more 10% sucrose solution than did control animals, indicative of diminished neophobia.

Thus, mice with increased vasopressin synthesis exhibited altered behavior consistent with enhanced attention and alertness but without change in learning and memory ability. These observations support prior data on vasopressin effects on cognitive function and suggest that the transgenic mice are a useful model for investigation of hormonal actions on the central nervous system.

Liver Diseases

69. **Plasma B-Carotene Correlates Positively with Alcohol Intake, but Is Decreased by Alcoholic Liver Disease.** S. Ahmed, M. A. Leo, C. S. Lieber. Alcohol Research and Treatment Center and Section of Liver Disease and Nutrition, Bronx VA Medical Center and Mt. Sinai School of Medicine, New York, NY.

Alcoholics have low fasting plasma β-carotene levels, probably due to poor dietary intake, but the possibility that alcohol might also have a more direct effect remained to be assessed.

Therefore, plasma carotenoids were determined by HPLC and their levels were compared with the average alcohol consumption over the preceding 3 months.

Whereas alcoholics had generally lower plasma β-carotene concentrations than controls, the heavy drinkers (>200 g/day) had about twice the β-carotene levels than those drinking less ($p < 0.01$). There was a significant correlation between plasma β-carotene and alcohol intake ($r = 0.6$, $p < 0.001$), even when the β-carotene values were expressed per plasma cholesterol, to correct for possible lipoprotein changes ($r = 0.67$, $p < 0.001$). Thus heavy alcohol consumption appeared to increase plasma β-carotene levels but, since it is associated with liver damage, the latter could also have played a role. To assess the influence of liver disease, β-carotene beadlets (30–60 mg per day) were given for three days to hospitalized alcoholics fed controlled diets. Patients with cirrhosis had a much lower plasma β-carotene response than those without; the latter in turn responded with lower β-carotene levels than controls (drinking <5 g ethanol/day). These differences were not eliminated by pancrease supplementation or when the values were corrected for plasma total or LDL cholesterol. Plasma retinol, α-tocopherol and other carotenoids (such as lycopene) did not differ significantly.

Conclusion. Plasma β-carotene is relatively increased by heavy alcohol consumption, whereas liver damage, especially cirrhosis, has the opposite effect. Malabsorption secondary to pancreatic insufficiency is apparently not responsible, nor can one incriminate lipid malabsorption, since other liposoluble compounds were not affected similarly. In these patients, β-carotene supplementation may be justified, but this should be coupled with control of drinking because of possible hepatotoxic alcohol/β-carotene interactions.

70. **3T3 Fibroblasts Transfected with an Aspartate Aminotransferase cDNA Express Both Plasma Membrane Fatty Acid Binding Protein and Saturable Fatty Acid Uptake.** LM Isola, S-L Zhou, C-L Kiang, DD Stump, and PD Berk. Depts. of Medicine & Biochemistry, Mt. Sinai School of Medicine, New York, NY 10029.

Uptake of long chain free fatty acids (FFA) exhibits kinetic features of facilitated transport in hepatocytes and certain other cells but not in fibroblasts. Several lines of evidence (Ann Rev Nutr 9:252) suggest that a 43 kDa plasma membrane fatty acid binding protein, FABPpm, is the FFA transporter. FABPpm, surprisingly, was found to be identical to the mitochondrial isoform of aspartate aminotransferase (mAspAT) (PNAS 87:3484; Stump DD, this meeting). To document its role in FFA transport, we constructed plasmid pMKAAT2, a modified pGEM3-Z containing a full length mAspAT cDNA downstream of a Zn^{++}-inducible metallothionine promoter.

3T3 fibroblasts were co-transfected with pMKAAT2 and pFR400, a plasmid conveying methotrexate (MTX) resistance, by $Ca_3(PO_4)_2$-DNA co-precipitation. Transfectants were selected in MTX, cloned, and exposed to increasing MTX concentrations to induce gene amplification. Stably transfected clones were characterized by Southern blotting; those with highest copy numbers of pFR400 alone (*pFR400*) or pFR400 plus pMKAAT2 (*pFR400/AAT*) were expanded for use in later studies. Cell surface expression of FABPpm was examined by immunofluorescence using rabbit anti rat liver FABPpm.

Neither untransfected 3T3 nor *pFR400* cells expressed surface FABPpm, though both exhibited punctate intracellular fluorescence, presumably in mitochondria. By contrast, plasma membrane immunofluorescence was clearly observed in *pFR400/AAT* cells, particularly after culture in 100 μM Zn^{++}. $[^3H]$-oleate uptake was studied by rapid filtration from media containing 500 μM BSA and 50–1000 μM total oleate (unbound oleate:6.5–430 nM). Initial velocities were determined over 45 sec, and the data fitted with the SAAM program to the sum of a linear plus a saturable function. Results (Table) indicate a 2-fold increase in Vmax (fmol/sec/50,000 cells) for oleate *pFR400/AAT* cells compared to *pFR400*, with a further 2.8-fold increase in presence of Zn^{++}. Zn^{++} had no effect in *pFR400* controls ($p > 0.5$). The 5.7-fold increase in Vmax between *pFR400* and *pFR400/AAT* in presence of Zn^{++} was highly significant ($p < 0.025$). Km's in *pFR400/AAT* and *pFR400* cells with/without Zn^{++} did not differ.

	uptake in pFR400		pFR400/AAT	
	−Zn	+Zn	−Zn	+Zn
Vmax	152 ± 24	141 ± 15	286 ± 97	809 ± 193
Km	113 ± 29	122 ± 22	106 ± 57	118 ± 50

Conclusions. mAspAT and FABPpm are identical, and mediate saturable FFA uptake.

71. **Serum Tissue Inhibitor of Metalloproteinase (TIMP) Is Increased in Precirrhotic and Cirrhotic Alcoholics and Can Serve as a Marker of Fibrosis.** J. Li, A. Rosman, M. Leo, Y. Nagai,* C. Lieber. Alcohol Research and Treatment Center, Bronx, VA Medical Center and Mount Sinai School of Medicine, Bronx, New York 10468. *Fuji Chemical Industries Ltd., Toyama, Japan.

Hepatic fibrosis reflects an imbalance between collagen production and degradation. One of the contributory factors to the development of hepatic cirrhosis is a decrease in collagenase activity (Maruyama et al., BBA 1981;658:121).

To determine whether this may be related to inhibition of tissue collagenase, TIMP was measured with a sandwich ELISA assay (Kodama, Matrix 1989;9:1) in the serum of 16 healthy controls and 42 alcoholic patients with biopsy proven liver disease, namely steatosis without fibrosis (N = 13), perivenular fibrosis (PVF, N = 12), and septal fibrosis and/or cirrhosis (N = 17). Liver biopsies were evaluated for fibrosis by a pathologist blinded to the clinical and laboratory features.

Serum TIMP values strongly correlated with fibrosis ($r_s = 0.74$, $P < 0.001$) and only modestly with inflammation scores ($r_s = 0.38$, $P < 0.01$). Compared to controls (mean value ± SEM, 177 ± 12 ng/ml), serum TIMP was significantly elevated in PVF (348 ± 27, $p < 0.005$) and in septal fibrosis and/or cirrhosis (458 ± 52, $P < 0.001$) but not in steatosis (204 ± 17, $P > 0.5$). Thus, the rise in TIMP does not appear to be a mere consequence of the cirrhosis, since it was present already at a precirrhotic stage. We also compared the diagnostic utility of serum TIMP to an RIA method of serum procollagen-III-peptide (PIIIP) measurement (Behring, Germany) another proposed marker of fibrosis. In contrast to serum TIMP, serum PIIIP was significantly elevated only in the septal fibrosis and/or cirrhosis group (1.41 ± 0.24 U/ml, $P < 0.01$) but not in the PVF (0.71 ± 0.10, $P > 0.5$) when compared to healthy controls (0.66 ± 0.03). It also was not increased in the steatosis group (0.56 ± 0.06). By defining the threshold as the upper value of the steatosis group (resulting in a specificity of 100%), serum TIMP was elevated in 50% of patients with PVF and 88% of patients with extensive fibrosis (septal fibrosis and/or cirrhosis). The overall sensitivity of serum TIMP for detecting either PVF or extensive fibrosis was significantly greater than that of serum PIIIP (72% vs. 41%, $P < 0.05$). At a specificity of 85% (i.e., 85% of alcoholics with steatosis have values below the selected threshold), the overall sensitivity for detecting either PVF or extensive fibrosis was 97% for TIMP vs. 72% for PIIIP ($P < 0.05$). Receiver operating characteristic (ROC) analysis was used to assess the abilities of the two tests to discriminate PVF or extensive fibrosis from steatosis. The area under the ROC curve for TIMP was significantly greater than for PIIIP (0.96 ± 0.03 vs. 0.79 ± 0.07, $P < 0.03$).

Conclusions. 1) serum TIMP is increased in alcoholic cirrhosis and may play a role in its pathogenesis through inhibition of collagenase activity. 2) In alcoholics, serum TIMP can serve as a marker of precirrhotic and cirrhotic states. 3) This test is more sensitive in detecting either PVF or extensive fibrosis and offers better discrimination from steatosis than serum PIIIP.

72. Phosphatidylcholine Corrects the Ethanol-Induced Decrease in Hepatic Phosphatidylethanolamine Methyltransferase (PEMT) Activity and Protects Against Cirrhosis. C. S. Lieber, S. Robins,* M. A. Leo. Alcohol Research and Treatment Center, Section of Liver Disease and Nutrition, VA Medical Ctr, Bronx, NY, Mt. Sinai School of Medicine, New York, NY and *VA Medical Ctr, Boston, MA.

Ethanol abuse results in striking membrane alterations which may play a key role in the pathogenesis of cirrhosis. Membranes consist mainly of phospholipids, primarily phosphatidylcholine. The synthesis of these lipids depends, in part, on PEMT, reported to be decreased in patients with cirrhosis. It is not known, however, whether this decline is a consequence of the cirrhosis or precedes it, and to what extent it is associated with phospholipid alterations. We also wondered whether dilinoleoyl phosphatidylcholine (which is highly bioavailable) can correct the enzyme defect as well as the ethanol-induced phospholipid abnormalities, and whether this could result in protection against cirrhosis.

This was studied in a baboon model of alcohol-induced cirrhosis. PEMT was measured in sequential percutaneous needle liver biopsies by the conversion of phosphatidylethanolamine to phosphatidylcholine, using radioactive S-adenosylmethionine.

Chronic alcohol consumption (1–6.5 yrs) resulted in the development of septal fibrosis in 10/12 baboons (with cirrhosis in 2); it significantly decreased hepatic phospholipids, phosphatidylcholine and PEMT already at non-fibrotic stages. These effects were fully prevented in 8 baboons supplemented with 2.8g/1000 kcal of a preparation rich in dilinoleoyl phosphatidylcholine. There were significant ($p < 0.001$) correlations between PEMT and either hepatic phosphatidylcholine ($r = 0.678$) or total phospholipids ($r = 0.662$).

Conclusions. 1) Alcohol consumption diminishes PEMT prior to the development of cirrhosis and decreases hepatic total phospholipids and phosphatidylcholine, key components of cell membranes; this may promote hepatocyte injury and thus trigger fibrosis. 2) Administration of dilinoleoyl phosphatidylcholine restores PEMT and corrects phospholipid and phosphatidylcholine depletions, thereby possibly contributing to the protection afforded by dilinoleoyl phosphatidylcholine against alcoholic liver injury and the ensuing cirrhosis. This striking protective effect of dilinoleoyl phosphatidylcholine against alcoholic cirrhosis in the baboon is now being verified in a multicenter, randomized, double-blind trial in man.

73. Alcohol Consumption Induces Fatty Acid ω-Oxidation, with a Greater Increase in Males than in Females. X. Ma, E. Baraona and C. S. Lieber. Alcohol Research & Treatment Center, Mount Sinai School of Medicine & Bronx VAMC, New York, NY.

Women are more vulnerable than men to develop alcoholic liver injury. Chronic ethanol administration to rats produced striking accumulation of non-esterified fatty acids in the liver of female, but not male, rats. This was associated with an ethanol-induced increase in cytosolic fatty acid binding protein (L-FABPc) and microsomal esterification much smaller in females than in males, despite similar inhibition of mitochondrial β-oxidation. Since products of ω-fatty acid oxidation have been found to increase both L-FABPc and peroxisomal β-oxidation, and ethanol induces microsomal activities, we wondered whether alcohol consumption induces cytochrome P450 4A1-mediated ω-oxidation and whether this response depends on gender.

To study this, 12 male and 12 female littermates of the same age were pair-fed liquid diets containing 36% of energy either as ethanol or as additional carbohydrate for 4 weeks. The initial step of ω-oxidation was assessed by the microsomal formation of 12-hydroxydodecanoic acid (measured by GC/MS) from lauric acid.

In the pair-fed controls, the rate of ω-hydroxylation was higher in females than in males ($p < .05$). However, ethanol feeding markedly increased the rate of ω-hydroxylation in males (248 ± 21 μg/30 min/g liver *vs* 131 ± 12 in controls; $p < .01$), but not in females (209 ± 16 *vs* 168 ± 19; N.S.). Since this process is catalized by cytochrome P450 4A1, we assessed the effects of ethanol feeding and gender on this cytochrome, using a sheep polyclonal IgG (kindly provided by Dr. G. Gibson), which specifically recognizes the P450 4A1. Scanning densitometry of Western blots from microsomal proteins revealed a 46% increase in P450IVA1 in ethanol-fed males ($p < .02$) with only 19% increase in the females. Despite competition of ethanol and ω-hydroxy fatty acids for alcohol dehydrogenase (ADH), the dicarboxylic acid products of this reaction accumulated in the liver of alcohol-fed male, but not female rats, probably due to the much higher affinity of ADH for ω-hydroxy fatty acids than for ethanol. These finding paralleled those on L-FABPc and fatty acid esterification, previously reported in similar treated rats.

In conclusion, alcohol consumption induces microsomal P450 4A1 and increases fatty acid ω-oxidation. By serving as an alternate oxidation pathway and by increasing fatty acid binding and esterification, the increase in ω-oxidation may compensate, at least part, for the deficit in fatty acid oxidation due to the ethanol-induced injury of the mitochondria, but less efficiently in females than in males, leading to potentially deleterious accumulation of free fatty acids in the female.

74. Recurrence of Hepatitis B Viral (HBV) Disease in Liver Transplant Recipients: Impact of Pre-Transplant HBV DNA Screening by Liquid Phase Hybridization Assay. A Min, A Borcich, L Leung, P Hytiroglou, S Emre, C Miller, S Thung, HC Bodenheimer. Depts. of Medicine, Pathology and Surgery, Mt. Sinai Medical Center, New York, NY.

Previous studies suggest almost universal recurrence of HBV disease following liver transplantation (OLT) in patients with active viral replication. However, HBV recurrence in patients who are serum HBV DNA negative pre-OLT has been less predictable. To further characterize HBV re-infection in such patients, we reviewed our experience over the period 1988–93 at Mount Sinai.

Methods. Of the 22 patients transplanted for chronic HBV disease, serum HBV DNA level post-OLT and/or follow-up (F/U) liver biopsy specimens were available on 19 patients (14M and 5F) surviving >1 month (mo). The mean duration of F/U for these 19 patients was 14.3 mo (range 1.3–39). The status of HBeAg, HBeAb and HBV DNA of the recipients was reviewed. Serum HBV DNA was measured using a liquid phase hybridization assay with negative cutoff at <1 pg/ml. No patient received immunoprophylaxis with IV HBIG.

Results. Mean age at time of OLT was 43.6 yrs (range 24–60). HBeAg was (–) in 17/18 patients (94%) tested. HBV DNA was (–) in 16/18 patients (89%). 15/19 patients are alive at a F/U of 15.5 mo (range 4.5–39). Histologic recurrence occurred in 11/19 patients (58%) at a mean of 6.0 mo post-OLT, but 7 patients (6 HBV DNA (–)) have no recurrence with a F/U of 16.6 mo (range 4.5–39). Four patients died (2 due to HBV) at a F/U of 9.8 mo (range 1.3–17). Of 16 patients who were HBV DNA (–) pre-OLT, HBV DNA remained undetectable in 8 patients (50%) up to 26 mo post-OLT; histologic recurrence occurred in 9/16 patients (56%) and 13/16 (81%) are alive at 15.2 mo F/U (range 4.5–39). Both patients who were HBV DNA (+) pre-OLT had histologic recurrence; 1 died of suicide and one is alive at 17 mo. Retransplants were done for primary nonfunction (4) and for hepatic artery thrombosis (1).

Conclusions. The absence of serum HBV DNA (<1 pg/ml) is associated with favorable early survival, and although disease recurrence is common, many patients (44%) remain free of HBV disease. The high rate of recurrent hepatitis indicates the need for effective anti-viral therapy post-OLT.

75. Why Does a More Concentrated Alcoholic Beverage Yield Lower Blood Alcohol Levels in the Fed State? Rajesh Sharma, M.D., R. Thomas Gentry, Ph.D., Zev Chayes, M.D., and Charles S. Lieber, M.D. Dept of Medicine, Mt Sinai School of Medicine and the Alcohol Research and Treatment Center, and Nuclear Med Service, Bronx VAMC, New York, NY.

Contrary to general expectations, more concentrated alcoholic beverages produce lower blood alcohol concentrations (BAC) than dilute beverages when both are consumed in the fed state (Roine et al., Alcoholism: Clin Exp Res 17:709–711, 1993).

To assess the role of gastric emptying, five healthy men were given alcohol (0.3 g/Kg, consumed as a 4% and 10% w/v solution in orange juice) with ^{99m}Tc-DTPA one hour after a standard meal.

The 10% alcohol significantly slowed gastric emptying (half-time 73 ± 10 min) compared to 4% alcohol (37 ± 4 min, $p < 0.01$). The absence of a significant effect using the same volumes without alcohol (half-time of 40 ± 5 min with 235 mL *vs* 35 ± 3 min with 588 mL, n.s.) demonstrated that the effect of concentration was a consequence of the alcohol and not the difference volume. To assess whether there was also an effect of alcohol concentration on the First Pass Metabolism (FPM) of alcohol (which occurs primarily in the stomach), eight subjects (including the 5 above) were given, on different days, the same dose of alcohol by intravenous infusion, and by oral consumption (4 and 10% w/v). The quantity of alcohol absorbed by the oral route was calculated by integration of the blood alcohol curves, using the *in vivo* elimination parameters obtained from the intravenous curve for each subject. This procedure, which is independent of rate of absorption (Gentry et al., Gastroenterology 92:A11, 1992), indicated that FPM (the difference between the quantity absorbed and the dose administered) increased from 28 ± 23 mg/Kg with 4% alcohol to 108 ± 12 mg/Kg with 10% ($p < 0.01$). This effect probably results from enhanced gastric ADH activity at higher ethanol concentrations as well as the prolonged exposure of alcohol to the gastric mucosa.

In conclusion, when consumed after a meal, a concentrated alcoholic beverage results in lower BACs than a dilute one because: 1) it is absorbed more slowly, and 2) more of the dose is metabolized by FPM, and thus less alcohol is absorbed.

76. Plasma Membrane Fatty Acid Binding Protein Is Identical to Mitochondrial Aspartate Aminotransferase. DD Stump, S-L Zhou, and PD Berk. Departments of Medicine and Biochemistry, Mount Sinai School of Medicine, New York, NY 10029.

Studies over the past decade have demonstrated that hepatocellular uptake of long chain free fatty acids (FFA) has the kinetic features of a facilitated transport process. A 43 kDa plasma membrane fatty acid binding protein (FABPpm), initially isolated at low yields by oleate-agarose affinity chromatography (FABP[1]; PNAS 82:4) has been proposed as the putative FFA transporter. Later methods for isolating FABPpm by salt extraction and HPLC (FABP[2]) gave higher yields of purer product; the isolated protein was found to be related structurally and immunologically to the mitochondrial isoform of aspartate aminotransferase (mAspAT), a soluble mitochondrial matrix protein with no known role in FFA metabolism (PNAS 87:3484). This conclusion has been challenged in reports claiming that FABP[1] and FABP[2] were not the same protein (Mol Cell Biochem 98;191).

To resolve this question, samples of FABP[1], FABP[2], and mAspAT were freshly isolated from rat liver, purified to homogeneity, and used to prepare polyclonal antisera in rabbits. The three protein preparations had an identical molecular size (43 kDa) on SDS-PAGE and gel permeation HPLC, had identical retention characteristics on four additional HPLC columns, and exhibited a similar pattern of multiple charge isoforms, pI ca 9.1, by isoelectric focusing. Electrophoresis under non-denaturing conditions also revealed no differences. Amino acid compositions of the preparations were similar within the resolution of the method, and N-terminal amino acid sequences were identical. FABP[1] bound FFA avidly. As initially isolated, FABP[2] and mAspAT bound FFA poorly; however, after retention on and elution from oleate agarose columns, both preparations bound FFA with affinity similar to FABP[1]. All three preparations were subjected to tryptic digestion, and the resulting peptides separated by reversed phase HPLC.

No differences in tryptic peptide patterns were observed among the three proteins. All three proteins produced a line of immunologic identity in agar gel diffusion studies employing the freshly prepared antisera. On Western blots, each reacted with antisera raised against the others.

We conclude that FABP[1], FABP[2] and mAspAT are indistinguishable. Transfection studies in 3T3 fibroblasts (Isola et al, this meeting) support this conclusion. How a single mature protein can be synthesized so that its distribution to two separate cellular locations is differentially regulated remains to be determined. Preliminary studies suggest this may occur at the transcriptional level by differential splicing.

77. Alcoholism Is Associated with Hepatitis C (HCV) but not Hepatitis B at the Bronx VA Medical Center. A. Waraich, A. Rosman, K. Galvia, R. Williams, F. Paronetto, C. Lieber. Alcohol Research and Treatment Center, Section of Liver Disease, and Pathology and Laboratory Medicine Service, Bronx VA Medical Center and Mount Sinai School of Medicine, Bronx, New York.

Previous studies have suggested an association of viral hepatitis with alcoholism. However, the role of confounding risk factors (intravenous drug use, blood transfusions) has not been adequately excluded.

We therefore performed HBsAg, anti-HBc, anti-HBs, and anti-HCV (by second generation ELISA) tests in 150 consecutive alcoholics admitted for detoxification and 111 randomly selected patients attending a general medical clinic who were also screened for alcoholism using the brief MAST and CAGE questionnaires. Of the 150 consecutive alcoholics, 50 had a history of intravenous drug abuse (IVDA), 11 had received blood transfusions (BT), and 89 denied any known risk factor for HCV. Of the 111 patients attending general medical clinic, 21 had a possible history of alcohol abuse, 14 had BT, and 76 denied any alcohol abuse, IVDA, or BT.

The overall anti-HCV seropositivity in actively drinking alcoholics was 36% and had a strong association with known risk factors (82% in IVDA, 27% in BT, contrasting to 11% in alcoholics without known HCV risk factors, $P < 0.001$). The overall hepatitis B seropositivity in alcoholics was 49% and had a strong association with IVDA (86% in IVDA vs. 46% in BT and 30% in alcoholics without known risk factors, $P < 0.001$). Four of the 150 alcoholics (2.7%) were HBsAg positive. The anti-HCV seropositivity in alcoholics without risk factors was significantly greater than in non-alcoholic patients without risk factors (11% vs. 1%, $P = 0.01$). In contrast, hepatitis B seropositivity in alcoholics without risk factors was not significantly different from the non-alcoholic group (29.5% vs. 30.3%, $P > 0.5$). Stepwise logistic regression analysis revealed that alcoholism was a significant risk factors for hepatitis C (adjusted odds ratio 7.6, 95% confidence interval 1.6–35.5, $P = 0.01$) but not for hepatitis B seropositivity ($P = 0.8$). In alcoholics without known HCV risk factors, there were no significant differences between anti-HCV positive vs. anti-HCV negative patients with regard to age, race, tatoos, and cocaine use. Anti-HCV positive alcoholics had higher serum admission AST (mean ± SEM, 121 ± 16 vs. 71 ± 6, $P < 0.001$) and ALT values (91 ± 15 vs. 54 ± 5, $P < 0.005$) compared to anti-HCV seronegative alcoholics. However, there were no significant differences in admission serum GGT values (258 ± 37 vs. 274 ± 59, $P > 0.8$) and serum AST/ALT ratio (1.60 ± 0.13 vs. 1.53 ± 0.09, $P > 0.6$) between the two groups.

In conclusion, hepatitis C but not hepatitis B seropositivity is increased in actively drinking patients without known risk factors, suggesting that alcoholism, in some way, is a predisposing factor for HCV infection. In addition, admission serum transaminases (but not serum GGT or the AST/ALT ratio) are higher in anti-HCV seropositive alcoholics than in anti-HCV negative alcoholic patients.

78. Kinetic Characterization of High Affinity, Cl$^-$ Dependent BSP Uptake in Isolated Rat Hepatocytes. K Wolfe, DD Stump, LM Isola, and PD Berk. Departments of Medicine and Biochemistry, Mount Sinai School of Medicine, New York, NY.

Published studies describe two seemingly distinct sinusoidal uptake systems for BSP: a "high affinity/low capacity" (reported Vmax 3–4 pmol/min/10^6 cells; Km < 0.3 μM) Cl$^-$ dependent system (system A) and a "low affinity/high capacity" (reported Vmax 3–7 nmol/min/10^6

cells; Km 2–14 μM) Cl^- independent system (system B). Both have been characterized under non-physiologic conditions. System B has been studied with hepatocyte suspensions in the absence of albumin; estimated kinetic parameters were subject to errors due to substrate depletion of $\leq 50\%$ during incubation. System A was studied exclusively in monolayer cultures at an unphysiologically low concentration of BSA; reported kinetic parameters were therefore subject to pseudofacilitation errors.

To better define the kinetic characteristics of system A, we have studied $[^{35}S]$-BSP uptake by hepatocyte suspensions from a medium consisting of 600 μM BSA, either in Hanks' buffer or in a buffer of similar cation composition in which Cl^- was replaced by other anions. BSP:BSA ratios ranged from 0.25:1 to 3:1, with corresponding unbound BSP concentrations (BSP_u) from 0.015 to 3.35 μM (JCI 45:281). Incubation volumes were chosen so that uptake depleted the media by $\leq 0.2\%$ of incubated substrate. $[^{35}S]$-BSP uptake was determined by rapid filtration; initial uptake velocities (V_o) were estimated by least squares fitting of the initial, 20 sec, linear portion of the uptake/time curve. The relationship between BSP_u and V_o was determined by fitting the data to physiologically relevant functions using the SAAM program.

Results. At all BSP_u studied, V_o was greater in the presence than in the absence of Cl^-. When the data were fitted to the Michaelis-Menten equation, as has been conventionally done, Vmax was significantly reduced and Km significantly increased in the absence, compared to the presence, of Cl^- (Vmax = 5.00 ± 0.48 vs 6.86 ± 0.28 nmol/min/10^6 cells, $p < 0.005$; Km = 0.691 ± 0.087 vs 0.405 ± 0.074 μM, $p < 0.01$). However, both in presence and absence of Cl^-, the best computer fit consisted of the sum of a saturable plus a linear component, which yielded quite different values for the kinetic parameters: Vmax = 1.77 ± 0.43 vs 2.42 ± 0.14 nmol/min/10^6 cells; Km = 0.207 ± 0.080 vs 0.094 ± 0.012 μM, without and with Cl^-, respectively.

Conclusions. Hepatocytes exhibit a high affinity Cl^- dependent BSP uptake system; its Vmax, however, is similar to that reported for the low affinity system. Valid comparisons with the low affinity system require new studies that avoid substrate depletion, pseudofacilitation and data fitting artifacts.

79. Differential Expression of the Plasma Membrane Transport System for Long Chain Free Fatty Acids in Obese Zucker Rats. S-L Zhou, DD Stump, LM Isola, ND Theise, and PD Berk. Departments of Medicine, Biochemistry and Pathology, Mount Sinai School of Medicine, New York, NY 10029.

Uptake of long chain free fatty acids (FFA) has the kinetic features of facilitated transport in hepatocytes, adipocytes, jejunal enterocytes and cardiac myocytes, but not in fibroblasts. A plasma membrane fatty acid binding protein, FABPpm, was proposed as a putative fatty acid transporter. In several experimental settings, changes in cell surface expression of FABPpm, measured by immunoassay, have correlated with changes in Vmax for cellular FFA uptake (e.g. JBC 267: 14456). To examine whether the FFA uptake system was regulated differentially in different tissues, we examined uptake of $[^3H]$-oleate by suspensions of intra-abdominal adipocytes and hepatocytes from homozygous obese (fa/fa) Zucker rats; heterozygous (Fa/fa) non-obese Zucker or normal Wistar rats served as controls.

All animals were 6–8 week old males. Studies were conducted in media containing 500 μM BSA and 50–1000 μM oleate; the unbound oleate concentration $[O_u]$ ranged from 6.5–430 nM. Uptake was determined by rapid filtration and initial uptake velocities computed over the initial 45 sec by least squares. All studies were performed at least in triplicate. Data were fitted to the Michaelis-Menten equation using the SAAM program.

Results were:

	Hepatocytes		Adipocytes	
	Vmax	Km	Vmax	Km
Obese (fa/fa)	3.0 ± 0.1	75 ± 5	60.0 ± 8.5	32.1 ± 7.5
Non-obese (Fa/fa)	2.3 ± 0.1	75 ± 3	10.3 ± 0.6	14.9 ± 1.9
Normal Wistar	N.D.	N.D.	7.6 ± 0.3	13.1 ± 1.2

only 30% in fa/fa animals compared to Fa/fa controls ($p < 0.005$); Km (nM unbound oleate) was unchanged. In adipocytes, the Vmax in fa/fa animals was increased by 480% vs non-obese Fa/fa ($p < 0.005$) and 690% vs Wistars ($p < 0.001$); Km's did not differ significantly between fa/fa and Fa/fa animals ($p > 0.05$). In H&E sections, hepatocytes from obese animals were normal in size and appeared to contain only minimal fat, although oil red O staining documented substantial lipid accumulation. By counting number of cells/10 randomly selected hpf in sections of abdominal fatty tissue, the radius of adipocytes from fa/fa animals was found to be increased by a mean of 44% compared to Fa/fa animals; the estimated doubling of surface area, 207%, was insufficient to explain the increase in oleate uptake Vmax.

Conclusions. These studies demonstrate that regulation of the saturable FFA transport system is tissue specific.

Molecular Medicine

80. Effects of Phospholipid Surface and Mass Transport on Factor X Activation by Tissue Factor-Factor VIIa Complex in a Continuous Flow Enzyme Reactor. Harry Andree, Paul Contino, Doris Repke, and Yale Nemerson. Division of Molecular Medicine and Department of Biochemistry, Mount Sinai School of Medicine, New York, N.Y.

The complex of the transmembrane protein tissue factor (TF) and coagulation factor VIIa is the primary initiator of blood clotting. The factor X activation rate of this complex was studied in the continuous flow reactor.

Capillary tubes were coated with membranes of 30% phosphatidylserine (PS) and 70% phosphatidylcholine (PC) containing TF. The activation rate of factor X was measured as a function of TF surface density. Due to the transport rate limited delivery of factor X towards the surface, saturation was observed.

At a wall shear rate of 1600 s^{-1}, half-maximal conversion of 150 nM factor X was reached at 3 fmoles TF-VIIa/cm^2, *i.e.* ≈0.04% of the surface covered with enzyme. The density that results in half-maximal saturation increased with substrate concentration and wall shear rate. The appearance of factor Xa at the outlet of the tube showed a large delay, explained by high-affinity binding of factor Xa to the phospholipid bilayer on the wall of the tube (K_d = 33 nM). At 70 fmoles TF-VIIa/cm^2, factor Xa was found to cover 80% of the phospholipid surface. Annexin V, a protein with high-affinity for phospholipids, displaces proteins from the surface and interferes with membrane mediated transport. TF-VIIa activity at high TF densities, could not be supressed by annexin V, which indicates that membrane mediated transport of factor X towards the enzyme complex is of limited importance. At dilute TF surface densities the inhibition increased up to 45%. Experiments at high TF-densities, with TF embedded into pure phosphatidylcholine membranes, resulted in a 70% reduction of activity.

This suggests an important role of PS for TF-VIIa activity. In cell membranes, loss of phospholipid asymmetry results in exposure of PS, and thus may enhance TF-VIIa activity.

81. Functional Expression of the Skeletal Muscle Ryanodine Receptor. Anne-Marie B. Brillantes, Karol Ondrias, Evgeny Kobrinsky, Andrew Scott, Barbara E. Ehrlich,* Andrew R. Marks. Molecular Medicine Program, Mount Sinai School of Medicine, NY, NY, *Department of Medicine, University of Connecticut, Farmington, CT.*

The molecular events leading to activation of the calcium release channel/ryanodine receptor (RyR) during excitation-contraction coupling in skeletal muscle remain poorly understood. To gain insight into the molecular basis of RyR function, we constructed a full-length (~15.2 kb) rabbit skeletal muscle RyR cDNA and functionally expressed it in *Xenopus* oocytes.

Functional expression of a calcium release channel was confirmed by activation of the endogenous Ca^{2+}-sensitive Cl^- channel in response to caffeine-induced intracellular calcium release (n = 30). Uninjected oocytes (n = 25) showed no response to 50 mM caffeine. The 565,000 MW cloned expressed RyR (confirmed by ^3H-Ryanodine binding, Northern and Western blot analyses) was purified using sucrose density gradients and reconstituted in planar lipid bilayers. Single channel recordings were performed to determine that the properties of the expressed channel matched those of the native skeletal RyR. It has been proposed that other molecules may be required for the RyR to form a functional calcium release channel.

The present study demonstrated that: (1) the RyR alone is sufficient to form a functional skeletal muscle SR calcium release channel; (2) the ligand binding sites for caffeine, ryanodine, calcium and ruthenium red are encoded by the RyR transcript.

82. Calcium Release Channel Expression in Human Heart Failure. Loewe O. Go, Kushal K. Handa, Tania M. Nanevicz, Adam L. Wilkes, Billie S. Fyfe, and Andrew R. Marks. Molecular Medicine Program, Mount Sinai School of Medicine, NY, NY.

The ryanodine receptor (RyR) is the major Ca^{2+} release channel (CRC) of cardiac and skeletal muscle activated during excitation-contraction coupling. The inositol 1,4,5-trisphosphate receptor (IP3R) is the major CRC of vascular smooth muscle and brain, activated hormonally via phosphoinositide turnover. In two previous studies we showed that RyR expression was decreased in end-stage human heart failure (Circ Res 1992; 71:18), and that the IP3R is expressed in rat cardiac myocytes (JCB 1993; 120:1137).

In the current study we examined CRC expression in failing and normal (NL) human hearts. RNA isolated from left atrial (LA) and left ventricular (LV) specimens obtained prospectively from patients undergoing cardiac transplantation ($n = 20$) and NL controls ($n = 4$) was analyzed using northern and slot blots. Quantification was with a phosphorimager, and CRC mRNA levels were normalized to 28S ribosomal RNA levels.

Northern blot analyses of human heart RNA detected a single ~15 kb mRNA with a 580 bp rabbit cardiac RyR cDNA probe, and a distinct ~10 kb mRNA with a 1.7 kb rat aortic smooth muscle IP3R cDNA probe. Compared to NL, RyR expression in failing hearts was again decreased in the LV (by 31%), but was increased in the LA (by 40%). In contrast, IP3R expression was increased in both LA and LV (by 30–50%).

We conclude that in contrast to the RyR, the IP3R mRNA is up-regulated in end-stage cardiomyopathy. This up-regulation may be compensatory by providing an alternative pathway for mobilizing intracellular Ca^{2+} release.

83. Effects of Adriamycin and Thyroxine on Calcium Release Channel Expression in a Rat Model of Heart Failure. Kushal K. Handa, Loewe O. Go, Maria T. Moschella, and Andrew R. Marks. Molecular Medicine Program, Mount Sinai School of Medicine, New York, NY.

Adriamycin-induced cardiomyopathy is a major toxic side effect which limits the use of this potent anti-tumor drug. The molecular basis for this drug-induced cardiomyopathy remains obscure; however, a generalized decrease in cardiac-specific gene expression occurs with adriamycin treatment. This is in contrast to thyroxine treatment which results in generalized increase in gene expression. Cardiac muscle contraction is an intricate process in which calcium release channels (CRCs) play a pivotal role. The entry of calcium through the voltage dependent calcium channel on the plasma membrane leads to the activation of the ryanodine receptor (RyR), the major CRC of cardiac muscle involved in excitation-contraction coupling. The inositol 1,4,5-trisphosphate receptor (IP3R) is another intracellular CRC recently found to be expressed in cardiocytes but whose functional significance is unclear.

An animal model of heart failure was established using adult rats by injecting a cardiotoxic dose of adriamycin (8 mg/kg intraperitoneally). The animals were then sacrificed 3, 6, 9, and 18 days after injection of adriamycin along with age and sex matched controls. Northern and slot blot analyses were performed on total RNA extracted from the rat hearts using the rat IP3R and rabbit cardiac RyR cDNA probes.

Compared to controls ($n = 12$), RyR expression was markedly decreased ~50% in the treated hearts ($n = 20$) at all time points, but there was a nonsignificant increase in IP3R expression. Preliminary data showed that thyroxine treatment (4 mg/kg) is associated with a four-fold increase in RyR expression. Simultaneous treatment with adriamycin and thyroxine appears to abolish these changes in RyR expression, but have an additive effect in increasing IP3R expression two-fold.

These results imply a role of the CRCs in heart failure and suggest that adriamycin-induced cardiomyopathy is mediated via altered CRC gene expression.

84. Modulation of Expression and Function of Putative Natural Killer (NK) Cell Inhibitory Receptors by Host Major Histocompatibility Complex (MHC) Class I Molecules. Franz M. Karlhofer, Rosemarie Hunziker, David H. Margulies, and Wayne M. Yokoyama. Molecular Medicine Division, Department of Medicine, Mount Sinai Medical Center, New York, NY, & Laboratory of Immunology, NIAID, NIH, Bethesda, MD.

The Ly-49 molecule is expressed on a subset (15–20%) of splenic $NK1.1^+$ cells from C57BL/6 or C57BL/10 ($H\text{-}2^b$) mice. The cytolytic activity of $Ly\text{-}49^+$ NK cells is specifically inhibited by target cell expression of $H\text{-}2D^d$ or an $H\text{-}2^k$ class I molecule, consistent with the possibility that Ly-49 directly engages these MHC class I molecules.

To determine the influence of host MHC molecules on Ly-49 expression, we examined splenic $NK1.1^+$ cells from MHC-congenic and transgenic strains of the B10 or B6 background by two-color flow cytometry.

$Ly\text{-}49^+$ NK cells were undetectable in F_1 hybrid and C57BL/10 MHC-congenic mice expressing the MHC class I molecules, D^d or D^k, and in a C57BL/6 strain transgenic for membrane bound D^d. In contrast, $Ly\text{-}49^+$ NK cells were detectable in two strains transgenic for soluble forms of D^d. $Ly\text{-}49^+$ NK cells are also absent in $B10.D2^{dm1}$ ($\alpha1^d\alpha2^{d/l}\alpha3^l$) mice. This demonstrates that the absence of $Ly\text{-}49^+$ NK cells depends on specific expression of α1/α2 domains of membrane bound D^d. $Ly\text{-}49^+$ NK cells are present in B10.AKM (K^k,D^q), and B10.S (K^s,D^s) mice and in C57BL/6 mice transgenic for a mutation in the β_2-microglobulin gene, confirming that Ly-49 expression is not restricted to the $H\text{-}2^b$ haplotype and suggesting that expression is not dependent on normal $H\text{-}2^b$ expression.

Although these studies suggest that $Ly\text{-}49^+$ NK cells may be permanently deleted by negative selection, analogous to T cell clonal deletion, $Ly\text{-}49^+$ NK cells can be cultivated in vitro from D^d-bearing mice, indicating that host MHC class I molecules modulate the expression of Ly-49 in a manner different from clonal selection. However, these $Ly\text{-}49^+$ NK cells are capable of killing a D^d-expressing transfectant, suggesting that the function of Ly-49 on these cells is also altered. Taken together, these data confirm our *in vitro* studies of Ly-49 specificity for MHC class I molecules. Moreover, these studies suggest that MHC class I molecules play important roles in the development of NK cells and establishment of the NK cell "repertoire."

85. Functional and Mutational Analysis of the *Drosophila Krüppel* Transcriptional Repressor. J. D. Licht, M. A. English, J. C. Reddy, M. Ro, R. Shaknovich, M. Grossel, W. Hanna and U. Hansen. Division of Molecular Medicine, Mount Sinai School of Medicine, New York, NY, and Dana-Farber Cancer Institute, Harvard Medical School, Boston, MA.

The *Drosophila Krüppel* (*Kr*) protein is a DNA-binding repressor of transcription in mammalian cells. (*Nature* 346: 76–9, 1990). The transcriptional repression and DNA-binding activities of the *Kr* protein can be dissociated and the repression function of *Kr* can be transferred to a heterologous DNA-binding protein, the *lac* repressor. Fusion genes between portions of the N-terminal region of the *Kr* protein and the *lac* repressor were assayed *in vivo* for their ability to repress transcription from a reporter gene containing *lac* operators upstream of the herpes thymidine kinase (*tk*) promoter.

We thus localized a repression region between amino acids 60 and 90 of the *Kr* protein. This portion of the *Kr* protein is predicted to form an alpha-helix with several hydrophobic faces.

However mutant proteins deleted for either the N-terminal or C-terminal portion of the protein were still able to repress transcription from a reporter gene containing *Kr* binding sites, suggesting the presence of redundant repression domains. Supporting this hypothesis, a fusion between the *lac* repressor and amino acids 402–502 of *Kr* repressed transcription from a *lac* operator containing reporter gene. In accordance with our prediction that alanine-rich regions of other *Drosophila* transcriptional factors would mediate transcriptional repression, a *lac* repressor *even-skipped* fusion was six-times more potent a transcriptional repressor than *lac-Kr*. The presence of a stretch of 11 alanines in a row as well as a proline-rich region in the *lac-eve* protein was required for repression.

Kr represses transcription when bound at kilobase distances upstream or downstream from the start site of *tk* transcription, suggesting function through protein-protein interactions with factors bound to the *tk* promoter. Low amounts of *Kr* co-transfected with a *Kr* binding site containing reporter gene do not lead to activation and a monotonic decrease in transcription is observed with increasing amounts of *Kr* expression plasmid. We examined the ability of the *Kr* protein to repress transcription activated by different *GAL4* fusion activators. *Kr* selectively repressed transcription activated by a *GAL4*-Sp1, a glutamine-rich activator protein but could not repress transcription mediated by the acidic activator *GAL4*. Correlating with this, we found that *Kr* and Sp1 proteins can associate in vitro. We currently believe that *Kr* functions to quench activation by glutamine-rich activation domains, perhaps by a direct protein-protein interaction, rather than by interfering with some component of the basal transcriptional machinery required for all transcriptional activation events.

86. PLZF, a Myeloid Specific Transcription Factor Rearranged with The Retinoic Acid Receptor in Acute Leukemia. J. D. Licht, A. Chen, Y. Wu, J. Li, M. A. English, R. Shaknovich, W. Miller, Jr., A. Scott, C. Willman, and S. Waxman. Divisions of Molecular Medicine and Medical Oncology, Mount Sinai School of Medicine, New York, NY, Memorial Sloan Kettering Cancer Center, New York, NY, and University of New Mexico, Albuquerque, NM.

Molecular analysis of a patient with acute promyelocytic leukemia revealed a translocation t(11;17) and a rearrangement between the gene encoding the retinoic acid receptor α (RARα) and novel gene called PLZF (*P*romyelocytic *L*eukemia *Z*inc *F*inger) (Z. Chen et al, 1993, S. Chen et al., 1993). The rearrangement yields two fusion proteins, one fusing the A domain, a transcriptional activation domain to 7 zinc fingers of PLZF. The other fusion protein contains the amino terminal region of PLZF including two zinc fingers and the B-F domains of RARα, including the DNA binding domain and ligand binding domain of the receptor. We have subsequently identified two additional patients with PLZF-RARα rearrangement and one of these patients had a novel site of rearrangement in the PLZF gene. PLZF is expressed in myeloid HL60 and NB4 cell lines, but not erythroid or lymphoid cell lines or the monocytoid U937 cell line. PLZF is expressed in the bone marrow of normal subjects as well as those with acute leukemia. In peripheral blood, PLZF is expressed in tissue macrophages but not in mature granulocytes. PLZF expression is down regulated during granulocytic differentiation of HL60 cells induced by retinoic acid and monocytoid differentiation induced by vitamin D3. Intriguingly, PLZF appears to be expressed in prostate cancer specimens but not in specimens from patients with benign prostatic hypertrophy. PLZF encodes a 673 amino acid protein with a predicted molecular weight of 74kd, containing 9 putative DNA-binding zinc finger motifs. When expressed in non-hematopoetic cells, the PLZF cDNA produces a ~80kd nuclear localized protein. The DNA binding activity and possible target genes of PLZF are under investigation.

To determine the transcriptional effector function of PLZF we fused the amino terminal portion of the protein to the DNA binding domain of the yeast *GAL4* protein.

This chimeric protein was a potent repressor of transcription of a test promoter containing *GAL4* DNA binding sites upstream of the herpes simplex virus thymidine kinase promoter.

This result suggests a possible mechanism for leukemogenesis by RAR-PLZF fusion; PLZF is normally a repressor of its target genes, but when fused to the A domain of the RAR becomes a constitutive activator. This may also explain why, in contrast to patients with t(15;17) APL the index patient as well as four other patients with the PLZF-RAR rearrangement failed to respond to retinoic acid or conventional chemotherapy.

87. Structural Organization of the Human Gene Encoding Nuclear Lamin A and Nuclear Lamin C. F. Lin and H. J. Worman. Division of Molecular Medicine, Dept. of Medicine and Brookdale Center for Molecular Biology, Mount Sinai School of Medicine, New York, NY.

The nuclear lamins are intermediate filament proteins of the nuclear envelope lamina. In most terminally differentiated mammalian cells, three major lamins termed lamin A, lamin B and lamin C are expressed. Lamin B is present in all cells whereas lamins A and C are absent from some undifferentiated and cancer cells. Lamins A and C are identical for the first 566 amino acids and differ in their carboxyl-termini. Lamin A is synthesized as a precursor called pre-lamin A which is isoprenylated. The last 18 carboxyl-terminal amino acids of pre-lamin A are proteolytically removed to generate lamin A. To better understand the above findings, as well as the evolution of the intermediate filament multigene family, we have determined the structural organization of the human gene that encodes nuclear lamins A and C.

Sequencing and restriction mapping show that the coding region spans approximately 24 kilobases (kb). The 5′ proximal promoter region contains several GC-rich stretches, a CCAAT-box and a TATA-like element of sequence TATTA. The lamin A/C gene contains 12 exons. Exon 1 codes for the amino-terminal head domain and the first part of the central rod domain common to lamins A and C. Exons 2–6 code for the remainder of the rod domain. Exons 7–9 code for the carboxyl-terminal tail domain sequences common to both lamin A and C; the sequence encoding the nuclear localization signal is contained in exon 7. Alternative splicing within exon 10 gives rise to two different mRNAs that code for pre-lamin A and lamin C. Exons 11 and 12 are lamin A-specific exons with the sequence coding for the CAAX-box isoprenylation motif in exon 12. As a consequence of alternative RNA splicing within exon 10, two proteins are generated, only one of which, pre-lamin A, can be modified by isoprenylation. The intron positions in the human lamin A/C gene are generally conserved in the previously characterized genes for Xenopus lamin LIII and mouse lamin B2, but differ from those in a Drosophila lamin gene. In the regions coding for the central rod domains, the intron positions are also conserved when compared to the intron positions in the genes for most cytoplasmic intermediate filament proteins except those for nestin and neurofilaments.

Analysis of the intron positions in these genes supports the hypothesis that the nuclear lamins and other intermediate filament proteins arose from a common ancestor. The lamin A/C gene is also the first example of how two different protein isoforms that differ in their capacity to be isoprenylated are generated by alternative RNA splicing.

88. The Characterization of Tissue Factor in Human Coronary Atheroma. Jonathan D. Marmur, Billie Fyfe, Samin K. Sharma, John A. Ambrose, Marc Habert, Sarah Eisenberg, Alan Lotvin, Douglas Israel, Sabino R. Torre, Yale Nemerson, Mark B. Taubman. Mt. Sinai Medical Center, NY, NY.

Tissue Factor (TF) initiates the predominant pathway of blood coagulation in vivo and has been detected in atherosclerotic plaque derived from carotid artery and saphenous vein grafts.

To characterize the expression of TF in coronary atheroma, immunohistochemistry with a monoclonal anti-human TF antibody was performed on frozen sections of 24 lesions from 24 patients treated with directional coronary atherectomy.

Positive staining for TF antigen was demonstrated in specimens derived from 8 (33%) of the lesions. TF antigen was distributed in a non-diffuse pattern, with small foci detectable predominantly in areas of acellular sclerotic plaque. Areas of intimal hyperplasia were not associated with positive TF staining. Differences between patients with positive TF stain (TF^+) versus patients with negative TF stain (TF^-) were analyzed using Fisher's exact test. Lesion morphology was defined as complex when an ulceration, irregular borders, or a filling defect was present on baseline angiography. All patients had 6 month clinical follow-up. Restenosis was defined as recurrence of symptoms with positive exercise perfusion imaging, or >50% diameter stenosis on angiography.

	TF+ (n = 8)		TF− (n = 16)
unstable angina (rest or post-MI pain)	7 (88%)		14 (88%)
thrombus on histology H&E staining	6 (75%)	p = 0.08	5 (31%)
complex angiographic morphology	6 (75%)	p = 0.03	4 (25%)
restenosis	3 (38%)	p = 0.36	3 (19%)

The association of TF antigen with a complex angiographic lesion morphology and the trend toward an association between TF antigen and histologic thrombus support a role for TF in the thrombotic events associated with coronary atherosclerosis.

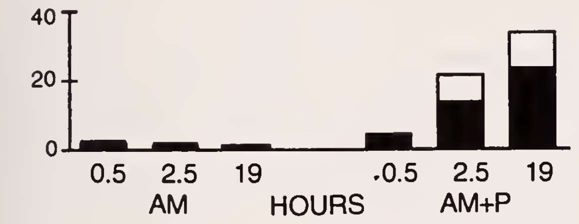
89. Detection and Quantification of Tissue Factor Activity in Coronary Atherectomy Specimens. Jonathan D. Marmur, Thiruvikraman V. Singanallore, Billie Fyfe, Samin Sharma, Arabinda Guha, Yale Nemerson. Depts. of Medicine and Pathology, Mt. Sinai Med. Ctr., NY.

Tissue factor (TF) is a membrane-bound clotting factor that initiates the major pathway of coagulation in vivo by binding factor VII (FVII). The TF:FVII complex converts factor X (FX) to its active form, Xa, thereby activating the clotting cascade. We have detected TF antigen in ≈⅓ of coronary atherectomy specimens using a monoclonal anti-TF antibody.

To detect and quantify TF activity, human coronary atherectomy specimens (n = 15) were incubated with an assay mix (AM) containing inactive FX (100 nM), FVII (1 nM), and calcium (5 mM) at 37°C in microtiter plate wells. In these conditions, the amount of Xa generation is determined by the quantity of bioavailable TF. To quantify Xa generation, a Xa-sensitive chromogen (ILeu-Pro-Arg-pNA) was added to the wells that produces a color change measured at 405 nM in an

ELISA counter. TF activity in wells containing AM alone, and AM and plaque (AM + P) were read after various periods of incubation.

TF activity (mean ± SD) is expressed in optical density units (milli OD) on the vertical axis:



Factor Xa generation was time-dependent and detectable at high levels in wells containing atherosclerotic plaque but not in wells containing AM alone. In AM alone wells (n = 15), the optical density was always <3 milli OD. At 2.5 hrs, 13 of the 15 (87%) atherectomy specimens generated >3.0 milli OD. Procoagulant activity at 0.5 hrs was eliminated by pre-incubation of the plaque with anti-TF antibody.

Conclusions. TF activity is detectable and quantifiable in coronary atheroma. The activity assay appears to be more sensitive than immunohistochemistry for the detection of TF (87% versus 33%). TF may constitute an important procoagulant molecule within the coronary atherosclerotic plaque.

90. Enhanced Expression of Tissue Factor in the Vessel Wall in Previously Injured versus Normal Artery Following Balloon Dilatation. Jonathan D. Marmur, Maria Rossikhina, Nicholas J. Gargiulo, Arabinda Guha, Milton Mendlowitz, Yale Nemerson, Mark B. Taubman. Mt. Sinai Hosp., NY.

The initiation of thrombosis after vascular injury occurs within minutes. We have recently demonstrated that tissue factor (TF) mRNA and activity are induced in normal rat aortic media at ≈2 hrs after balloon injury, suggesting that acute activation of the TF gene may play a role in the thrombus propagation. In the rabbit aorta balloon injury model it has been shown that in comparison to balloon dilatation of a normal artery, balloon dilatation of a previously injured artery that has developed a neointima is associated with a marked increase in fibrin deposition.

To examine the role of TF in the re-injury model, rat aortas were subjected to a second balloon injury 2 weeks after the first (n = 3 rats/time point). Rat aortic TF mRNA was examined by Northern blot analysis and in-situ hybridization. TF activity was measured using a recently developed colorometric assay of factor Xa generation and is expressed in arbitrary TF units/mg of total protein (U/mg; mean ± SD). Total protein was determined using the Bradford reagent.

After a single injury, rat aortic TF mRNA and activity were elevated at 2 hours compared with control (101 ± 21 vs 29 ± 10 U/mg), and returned to baseline by 24 hours. At 2 weeks, no increase in TF mRNA or activity was seen and intimal hyperplasia was consistently present. After a second injury TF activity was induced within 30 minutes (88 ± 14 U/mg) and peaked at 1 hr to higher levels than those seen after a single injury (202 ± 47 U/mg). Mural thrombus was detectable on light microscopy after double injury but not after single injury.

In previously injured vessels with a neointima, induction of TF expression in arterial media occurs more rapidly and to a greater degree than in normal artery. Injury to diseased vessels, such as that seen during coronary angioplasty, may involve an enhanced expression of TF that participates in thrombus initiation.

91. Intracoronary Thrombin Generation and Activity During Angioplasty (PTCA). Jonathan D. Marmur, Samin K. Sharma, Neda Khaghan, Fred Resnick, Kenneth Bauer, Sabino R. Torre, Robert D. Rosenberg, John A. Ambrose. Mt. Sinai School of Medicine, New York, NY; Beth Israel Hospital, Harvard University, Boston, MA.

Initiation of the clotting cascade ultimately results in the conversion of fibrinogen to fibrin and of prothrombin to thrombin. Fibrinopeptide A (FPA) and prothrombin fragment F_{1+2} (F_{1+2}) are released by these processes, respectively, and have been used as biochemical markers of coagulation cascade activity. We have previously shown that in systemically heparinized patients, levels of FPA and F_{1+2} may be accurately determined in samples withdrawn through a PTCA catheter.

To monitor the activation of thrombosis during PTCA, we collected blood samples before (Pre-PTCA) and 10 minutes after the final balloon inflation (Post-PTCA) in 39 patients. Samples were taken simultaneously from a femoral venous sheath (VN) and from the PTCA catheter (AR), which was placed proximal and distal to the lesion for Pre- and Post-PTCA sampling, respectively. Plasma levels (mean ± SD) were determined by radioimmunoassay and compared using a paired, two-tailed t-test.

	FPA (ng/mL)	F1+2 (nmol/L)
VN		
Pre-PTCA	5.22 ± 3.49} p < 0.001	0.804 ± 0.677} p = 0.56
Post-PTCA	4.52 ± 4.86}	0.853 ± 0.710}
AR		
Pre-PTCA	3.01 ± 2.59} p = 0.19	0.771 ± 0.395} p = 0.26
Post-PTCA	4.13 ± 4.06}	0.936 ± 0.866}

In the setting of decreasing systemic levels of FPA, as demonstrated by the results from venous sampling, coronary blood FPA levels show an increasing trend. PTCA increases thrombin activity within the coronary artery at the site of balloon injury, despite the systemic effects of heparin.

92. FK-506 Binding Protein Is Tightly Bound to the Ryanodine Receptor in the Heart. Roxana Mehran, Anne-Marie Brillantes, T. Jayaraman, Karol Ondrias and Andrew R. Marks. Department of Medicine, Molecular Medicine Program, Mount Sinai School of Medicine, New York, N.Y.

The calcium (Ca) release from sarcoplasmic reticulum (SR) is comprised of four ryanodine receptors (RyR). The RyR is activated during excitation-contraction coupling in cardiac and skeletal muscle. We have previously shown that FK-506 binding protein (FKBP12) is physically associated with RYR isolated from rabbit skeletal muscle SR in a molar ratio of one FKBP12 to two RyRs.

Northern blot analysis using an FKBP12 cDNA probe showed that the 1.6 kb mRNA is expressed in skeletal and cardiac muscle. We cloned the full length human cardiac FKBP cDNA from a human ventricular λgGT10 cDNA library.

Sequence analysis demonstrated that the FKBP12 expressed in human heart is encoded by the same gene as the human T lymphocyte FKBP12. Immunoprecipitation of cardiac RYR using an anti-FKBP12 antibody demonstrated a physical association between the two molecules. Western blot analysis using an antibody directed against the amino terminus of FKBP12 showed that FKBP12 was present in skeletal and cardiac SR and in highly purified RyR preparations. Addition of recombinant FKBP12 to cloned expressed skeletal muscle RYR reconstituted in planar lipid bilayers demonstrated that FKBP12 stabilizes the cloned expressed RyR and increases channel opening.

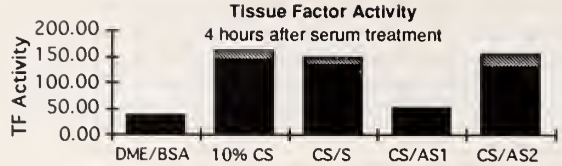
Thus, we have shown that the Ca release channel of cardiac and skeletal muscle consists of a complex which includes four of the 565,000 Da RyRs and two FKBP12 (12,000 Da each). FKBP12 appears to optimize the function of the SR Ca release channel involved in EC coupling.

93. Antisense Oligonucleotide Inhibition of Tissue Factor-Induced Coagulation. Steven A. Nichtberger, Claire-Lise Rosenfield, Yale Nemerson, Mark B. Taubman. Divisions of Cardiology, Molecular Medicine and Thrombosis. Mt. Sinai School of Medicine, NY, NY.*

Tissue factor (TF) is a transmembrane glycoprotein that is the primary initiator of coagulation. We have reported that TF mRNA and activity are highly regulated in cultured vascular smooth muscle cells (VSMC) by growth factors, a clotting factor, and in rat aortic media after balloon injury. These observations suggest that induction of TF may be important in thrombosis associated with myocardial infarction and coronary angioplasty.

As a first step toward elucidating the role of TF induction in vascular injury, we have examined the effect of antisense oligonucleotides (AS) on TF expression in cultured rat aortic VSMC.

TF mRNA (assayed by Northern blot analysis) and activity (assayed in 96 well dishes by a chromogenic assay that measures the conversion of factor X to Xa) were barely detectable in quiescent VSMC (grown in serum-free medium (DME/BSA) for 48 h). Following stimulation with 10% calf serum (CS), levels of TF mRNA increased at 15 min, peaked at 60–90 min (≈3000 copies/cell), and returned to baseline by 3 h. TF activity increased at 30 min, peaked at 2–8 h (≈5–10-fold), and returned to baseline by 24 h. AS flanking the initiation ATG (AS1) blocked the serum-induced rise in TF activity (>85% inhibition).



4 h incubation with AS1 prior to serum treatment was required for inhibition. Maximal inhibition was seen at 20 μM AS1 and the effect persisted for 24 h. The corresponding sense oligonucleotide(S) or an AS containing a single base mismatch (AS2) failed to inhibit TF expression.

We conclude that AS1 treatment is effective in blocking coagulation mediated by TF, in spite of its expression at very high levels, in cultured VSMC.

94. Autoantibodies Against Nuclear Pore Membrane Glycoprotein GP210 in Patients with Primary Biliary Cirrhosis Recognize an Epitope with Sequence Homology to Bacterial Polypeptides. R. E. Nickowitz and H. J. Worman. Division of Molecular Medicine, Dept. of Medicine and Brookdale Center for Molecular Biology, Mount Sinai School of Medicine, New York, NY.*

Patients with primary biliary cirrhosis (PBC) have autoantibodies against gp210, the major glycoprotein of the nuclear pore membrane. Gp210 is composed of a 1808 amino acid amino-terminal domain that is located in the perinuclear space, a single transmembrane segment and a 58 amino acid carboxyl-terminal domain that is located on the nucleo-cytoplasmic side of the nuclear pore membrane. We have determined the epitope(s) of gp210 that is recognized by autoantibodies from patients with PBC.

Twelve glutathione-S-transferase fusion proteins containing different regions of gp210 were expressed using the prokaryotic expression vector pGEX-2T and purified by glutathione-Sepharose chromatography. The fusion proteins were used in immunoblotting experiments with serum from 25 patients with PBC that had autoantibodies against gp210.

None of the autoantibodies recognized the amino-terminal domain of gp210 located in the perinuclear space. All 25 autoantibodies recognized the 58 amino acid nucleocytoplasmic domain. Immunoblotting of fusion proteins that contained different regions of the nucleocytoplasmic domain showed that autoantibodies from all 25 patients only recognized fusion proteins that contained the sequence NH_2-PPSGLWSPAY. When compared to available protein sequences, homology was found between the recognized epitope of gp210 and a sequence common to the protein products of the *E. coli* mutY gene and the *S. typhimurium* mutB gene:

```
          gp210 epitope:        PPSGLWSPAY
                                !!!!!!   !
E. coli mutY gene product:  LLAQRPPSGLWGGLYCFP
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These findings demonstrate that autoantibodies against gp210 in patients with PBC only recognize a restricted region in the protein's nucleo-cytoplasmic domain. The epitope is homologous to a portion of the *E. coli* mutY gene product suggesting that these autoantibodies may arise by molecular mimicry of bacterial antigens. As homologies between the *E. coli* and human E2 subunits of pyruvate dehydrogenase have also been demonstrated, the present data again raise the provocative question: is there evidence for molecular mimicry in PBC?

95. Autoantibodies Against Recombinant Integral Membrane Proteins of the Nuclear Envelope in Patients with Primary Biliary Cirrhosis. R. E. Nickowitz, R. W. Wozniak, F. Schaffner and H. J. Worman. Division of Molecular Medicine and Division of Liver Diseases, Dept. of Medicine and Brookdale Center for Molecular Biology, Mount Sinai School of Medicine, New York, NY and Laboratory of Cell Biology, The Rockefeller University, New York, NY.

An assay utilizing recombinant polypeptides was designed to detect serum autoantibodies against two integral membrane proteins of the nuclear envelope, gp210 and the lamin B receptor. The data were analyzed to determine the significance of these autoantibodies in the diagnosis of primary biliary cirrhosis (PBC).

Serum samples were obtained from 159 patients with PBC and 46 controls with viral hepatitis, autoimmune hepatitis, or other diseases from the inpatient and outpatient services of The Mount Sinai Hospital. Recombinant fusion proteins of nuclear pore membrane glycoprotein gp210 and inner nuclear membrane protein lamin B receptor were expressed using the pGEX-2T vector.

Autoantibodies against recombinant gp210 were detected in 15 of 159 patients with PBC and 0 of 46 individuals who were either healthy or had other diseases. Antibodies against recombinant lamin B receptor were detected in 2 patients with PBC and 0 control individuals. The presence of autoantibodies against these proteins had a sensitivity of 11% and specificity of 100% for the diagnosis of PBC. Autoantibodies against gp210 were present in 4 of 19 (21%) patients with PBC who did not have detectable antimitochondrial antibodies. Patients with PBC and serum antibodies against gp210 had a significantly higher incidence of associated rheumatoid arthritis than patients without these antibodies. The two groups did not otherwise differ in age, sex, routine laboratory values, serum IgM concentrations or incidences of associated diseases other than arthritis.

The results show that autoantibodies against gp210 and the lamin B receptor, integral membrane proteins of the nuclear envelope, are present in 11% of patients with PBC and can be unequivocally identified by an assay utilizing recombinant polypeptides. These autoantibodies have a specificity of 100% for the diagnosis of PBC and may be particularly useful in diagnosing patients without detectable antimitochondrial antibodies. They may also identify a subgroup of patients that has an increased incidence of associated rheumatoid arthritis.

96. Identification and Characterization of Novel Nuclear Envelope Proteins Using Autoantibodies from Patients with Autoimmune Liver Diseases. C. M. Noyer, R. E. Nickowitz and H. J. Worman. Division of Molecular Medicine, Dept. of Medicine and Brookdale Center for Molecular Biology, Mount Sinai School of Medicine, New York, NY.

Autoantibodies from patients with primary biliary cirrhosis (PBC) and autoimmune hepatitis (AH) frequently recognize proteins of the nuclear envelope. Autoantibodies from patients with AH generally recognize the nuclear lamins and those from patients with PBC recognize gp210 and the lamin B receptor, integral proteins of the inner nuclear membrane.

We have screened serum samples by immunofluorescence microscopy for autoantibodies that recognize the nuclear envelope.

Autoantibodies from 47 of 159 patients with PBC and 6 of 14 patients with AH gave nuclear rim fluorescence when examined by immunofluorescence microscopy, suggesting nuclear envelope reactivity. Of the 47 samples from patients with PBC, 17 recognized integral membrane proteins gp210 and lamin B receptor and 4 recognized lamins. Of the 6 samples from patients with AH, 3 recognized nuclear lamins. Autoantibodies from one patient with AH reacted with a protein of approximately 60 kDa on immunoblots of proteins from rat liver nuclear envelopes that was different from nuclear lamins, lamin B receptor or other previously characterized antigens. In the samples from the patients with PBC, two contained autoantibodies that recognized a protein in rat liver nuclear envelopes with an apparent molecular mass of 47 kDa. One sample contained autoantibodies against a protein of apparent molecular mass 63 kDa on immunoblots of rat liver nuclear envelope proteins. Autoantibodies purified from these serum samples by affinity chromatography against the recognized proteins labeled the nuclear periphery when examined by immunofluorescence microscopy. Both of these apparently novel protein antigens were not extracted from nuclear envelope preparations with 1 M NaCl but were extractable with 8 M urea.

These results confirm that autoantibodies from numerous patients with autoimmune liver diseases recognize proteins of the nuclear envelope. Several of these patients contain autoantibodies that recognize novel proteins of this organelle that are presently being characterized in greater detail.

97. Transcriptional Activation and Repression by the Wilms' Tumor (WT1) Gene Product. J. C. Reddy, J. C. Morris, M. A. English, D. A. Haber, X. N. Luo, G. Atweh and J. D. Licht. Divisions of Molecular Medicine, Hematology and Neoplastic Diseases, Mount Sinai Medical Center, New York, NY 10029 and Massachusetts General Hospital Cancer Center, Charlestown, MA 02114.

The WT-1 gene product binds to the DNA sequence 5′-GCGGGGGCG-3′, also recognized by the product of the EGR-1 and EGR-2 genes and was previously shown to be a transcriptional repressor. (Madden et. al., 1991; Drummond et. al., 1992) In contrast with these results, we found that the WT1 gene product, when expressed in African green monkey kidney (CV-1) cells and early passage NIH 3T3 cells, activated transcription from a reporter gene containing EGR-1 binding sites up to 90-fold.

Transcriptional activation was dose dependent in both cell lines and did not plateau or decrease at high input levels of plasmid, suggesting that the transcriptional machinery for activation by WT-1 is not limiting in the cell. An alternatively spliced form of the WT1 gene WT1(B) which inserts a serine rich amino acid segment was a more potent activator than WT1(A), lacking the insert. WT1 forms C and D which contain a three amino acid insert (+ KTS) between the third and fourth zinc fingers of the protein are known not to bind to the EGR site and did not affect transcription from the reporter gene itself but significantly blocked the ability of WT1(A) to activate transcription. WT(AR), (Haber et. al., 1991) a naturally occurring mutant, also prevented transcriptional activation by WT-1 suggesting a dominant negative activity on the action of the wild-type protein.

These data suggest the formation of an inactive heterodimer between alternatively spliced forms of WT1 or mutant and wild type forms as a mode to regulate the net transcriptional activity of WT1.

We also studied the ability of WT1 to affect transcription of the promoter of the P18 gene, which as is the case for WT1 is highly expressed in leukemic blast cells. WT1 forms A and B activated this promoter while forms C and D repressed the promoter. A deletion mutant of the promoter, which eliminated GC rich sequences downstream of the start site of transcription was still activated by forms A and B but could no longer be repressed by C and D.

This suggests the possibility of a (+ KTS) form specific element in the P18 promoter and also supports the notion that *cis*-acting elements both 5′ and 3′ to the start site of transcription are required for WT1 protein to repress transcription.

98. **Structural Organization and Expression of the Human Gene Encoding the Inner Nuclear Membrane Lamin B Receptor.** E. Schuler, F. Lin and H. J. Worman. Division of Molecular Medicine, Dept. of Medicine and Brookdale Center for Molecular Biology, Mount Sinai School of Medicine, New York, NY.

The lamin B receptor (LBR) is an integral membrane protein of the inner nuclear membrane that was originally characterized in birds and subsequent in humans. It has been proposed that LBR anchors the nuclear lamina to the inner nuclear membrane by binding to lamin B in interphase and targets vesicular remnants of the inner nuclear membrane to decondensing chromosomes at the end of mitosis to initiate nuclear envelope reassembly. LBR has a basic nucleoplasmic amino-terminal domain followed by eight putative transmembrane segments and displays no overall homology to other proteins of known sequence. We have now determined the structural organization of the human gene that codes for this unique nuclear envelope protein.

Sequencing and restriction mapping of overlapping genomic clones show that the human LBR gene spans more than 50 kilobases (kb). One transcription start site is located 3 kb 5′ to the initiation AUG. The RNA segment in this region that is spliced from most transcripts may contain an alternative promoter and transcription start site. The coding region of the LBR gene contains 11 exons. Three exons encode the nucleoplasmic amino-terminal domain and eight exons encode that putative transmembrane segments. An intron separates the portion of the gene encoding the amino-terminal domain from the portion encoding the transmembrane segments. A yeast gene has been identified coding for a protein that is homologous to the transmembrane portion of LBR but lacking the amino-terminal domain.

This finding raises the possibility that LBR arose in evolution by the recombination of such an ancestral gene, encoding a polytopic membrane protein, and another gene, encoding a soluble nuclear protein. LBR mRNA and protein was detected in several cell lines of different embryonal origin but at various amounts, suggesting regulated expression of the LBR gene. The present results represent the first determination of the structural organization of a gene that codes for an integral membrane protein of the inner nuclear membrane.

99. **The Polymorphic LY-49 Family of Cell Surface Molecules Expressed by Natural Killer (NK) Cells.** Hamish R. C. Smith, Brian F. Daniels, Franz M. Karlhofer, and Wayne M. Yokoyama. Molecular Medicine Division, Department of Medicine, Mount Sinai Medical Center, New York, NY 10029 and VA Medical Center, San Francisco, CA 94121.*

We have recently demonstrated that the murine Ly-49 molecule is a primary determinant of NK cell specificity. Ly-49 appears to interact with polymorphic regions of major histocompatibility class I molecules on target cells and globally inhibit NK cell activity. However, Ly-49 is expressed only by a subset (20%) of NK cells. If the interaction between Ly-49 and MHC class I represents a paradigm for understanding NK cell specificity and putative inhibitory NK cell receptors, NK cells that do not express Ly-49 should express other molecules, perhaps related to Ly-49, that provide the inhibitory receptor function. To examine this question, we used a full-length Ly-49 cDNA probe to screen a cDNA library, prepared from oligo-dT-primed poly$(A)^+$ mRNA from IL-2-activated NK cells.

Multiple clones were isolated and sequenced. All cDNAs distinct from Ly-49 cDNA were analyzed in detail. If necessary, sequences were extended by anchored-PCR of 5′ regions.

These cDNAs were homologous to the Ly-49 cDNA with mismatches scattered throughout the sequences, indicating that they were derived from distinct genes. The cDNAs were not allelic variants because all cDNAs were isolated from C57BL/6-derived cells. All cDNAs predicted type II integral membrane proteins homologous to Ly-49. Based on nucleotide homology, the cDNAs could be segregated into five groups; one with Ly-49 cDNA itself (now termed Ly-49A) and four other groups containing individual distinct sequences encoding polypeptides with 64–76% amino acid identity with Ly-49A. The final group comprised 3 cDNAs that shared identical sequences but differed from each other in coding or untranslated regions by deletions or insertions of short DNA segments. By immunoprecipitation analysis with an anti-peptide antiserum directed against a conserved portion of the Ly-49A amino (intracellular) terminus, we demonstrated that Ly-49^- NK cells express Ly-49-related molecules.

Thus, NK cells express polymorphic molecules related to Ly-49A. Further analysis of the expression and function of these molecules should provide significant insight into NK cell specificity.

100. **Regulation of Osteopontin (OPN) mRNA in Vascular Smooth Muscle Cells (VSMC).** Andrea S. Weintraub, Robert S. Green, Claire-Lise Rosenfield, Mark B. Taubman. Mt. Sinai School of Medicine, Dept. Pediatrics and Medicine, N.Y., N.Y.

Atherosclerotic coronary artery disease is characterized by increased growth and migration of VSMC, resulting in intimal hyperplasia and stenosis. Platelet-derived growth factor (PDGF), a potent mitogen and chemoattractant for VSMC, is felt to play a role in the response of VSMC to injury. To elucidate the mechanisms underlying PDGF-activation of VSMC, we have attempted to identify PDGF-inducible genes.

A rat aortic VSMC cDNA library was screened with cDNA from quiescent (treated with 0.4% calf serum for 48 hr) and PDGF-stimulated cells. Six clones were identified which demonstrated increased hybridization to PDGF-stimulated cDNA.

The nucleotide sequence of one clone containing ~1.5 kB insert was homologous with rat OPN. OPN is a secreted protein involved in matrix organization in bone and non-osteogenic tissues. Quiescent VSMC expressed very low levels of OPN mRNA. 10% calf serum induced high levels of OPN mRNA beginning at ~2 hr. PDGF (10 ng/ml), angiotensin II (1×10^{-6} M), and basic fibroblastic growth factor (10 ng/ml) also produced a rapid induction of OPN mRNA; levels remained elevated for 48 hr. TGF-β, which generally inhibits growth of cultured VSMC, did not induce OPN mRNA.

These data suggest that stimulation of VSMC growth is accompanied by increased OPN expression. The role of OPN in the vasculature is unknown; its induction by growth agonists raises the possibility that it may be involved in the regulation of VSMC growth, possibly by providing the appropriate extracellular milieu.

101. **Primary Structure of the Human Inner Nuclear Membrane Lamin B Receptor and Interactions of the Expressed Protein with Lamin B and DNA.** Q. Ye and H. J. Worman. Division of Molecular Medicine, Dept. of Medicine and Brookdale Center for Molecular Biology, Mount Sinai School of Medicine, New York, NY.

The lamin B receptor (LBR) is an integral membrane protein of the inner nuclear membrane that was originally characterized in birds. It has been proposed that LBR anchors the nuclear lamina to the inner nuclear membrane by binding to lamin B in interphase. It has also been hypothesized that LBR targets vesicular remnants of the inner nuclear membrane to decondensing chromosomes at the end of mitosis to initiate nuclear envelope reassembly in the daughter cells.

To further test these hypotheses and also establish if LBR is a protein common to other vertebrate species, we have isolated cDNA clones for human LBR, determined its primary structure and examined the lamin B and DNA binding properties of expressed LBR polypeptides.

Human LBR is 68% identical to chicken LBR. It has a nucleoplasmic amino-terminal domain 210 amino acids in length followed by eight putative transmembrane segments. The amino-terminal domain is basic, has several DNA-binding motifs and contains consensus sites for phosphorylation by protein kinase A and $p34^{cdc2}$ protein kinase that are conserved in chickens and humans. A fusion protein containing the amino-terminal domain of human LBR can precipitate lamin B from nuclear extracts of rat hepatocytes demonstrating that the nucleoplasmic domain binds to lamin B. This fusion protein also binds to DNA on "Southwestern blots" and retards the migration of viral DNA on agarose gels. Heat denaturation and protease treatment abolishes the ability of the protein to bind to DNA. Like chicken LBR, human LBR also undergoes mitosis-specific phosphorylation by $p34^{cdc2}$ protein kinase that could hypothetically modulate lamin B and DNA binding activities at different times in the cell cycle.

These data confirm that LBR is conserved among vertebrate species. The nucleoplasmic amino-terminal domain of LBR can bind to lamin B and DNA in vitro, consistent with LBR's proposed functions of anchoring the lamina to the inner nuclear membrane in interphase and in targeting inner nuclear membrane-derived vesicles to decondensing chromosomes during nuclear envelope reassembly at the end of mitosis.

Renal

102. Cation Transport in MDCK Cells Transfected with Tamm-Horsfall Protein (THP). D. Kaji, J. Bates, J. Goyzueta, H. Yu, V. Sukhatme and S. Kumar. Renal Division, Department of Medicine, VA Medical Center, Bronx, NY, and Mount Sinai Medical Center, New York, NY; University of Chicago, Chicago, IL; Beth Israel Hosp, Boston, MA; and W. K. Warren Institute, University of Oklahoma, Oklahoma City, OK.

To examine whether expression of THP alters transport in renal epithelial cells, we examined K influx in wild type MDCK cells (MD-WT), MDCK cells transfected with THP using SV40 promoter (MD + 1), or a cytomegalovirus (CMV) promoter (MD + 2) and MDCK cells transfected with a control plasmid containing only the CMV promoter but no THP (MD-1).

Expression of THP was confirmed by Northern blots and immunocytochemistry. K influx, measured with ^{86}Rb in media containing (in mM) NaCl 145, KCl 5, glucose 5, pH 7.4 at 37°C, with or without inhibitors, was expressed as μmol · mg protein^{-1} · hour^{-1}. Means ± SD of K influx, n = 6.

	MD-WT	MD + 1	MD +2	MD − 1
Total	0.64 ± 0.04	0.29 ± 0.03	0.24 ± 0.03	0.29 ± 0.03
Ouabain sensitive	0.34 ± 0.05	0.16 ± 0.06	0.11 ± 0.01	0.13 ± 0.03
Bumetanide sensitive	0.23 ± 0.03	0.09 ± 0.04	0.09 ± 0.04	0.13 ± 0.02
Ouabain and bumetanide resistant	0.06 ± 0.04	0.03 ± 0.01	0.04 ± 0.01	0.03 ± 0.01

Ouabain and bumetanide resistant K influx was not different in all groups. Ouabain sensitive and bumetanide components of K influx, mediated by Na-K pump and NaK2Cl cotransport respectively, were decreased in cells transfected with THP using SV40 or CMV promoter ($p < 0.005$ compared to MD-WT). However, both ouabain and bumetanide sensitive components of K influx were also reduced in MD-1, cells transfected with the control plasmid containing only the CMV promoter ($p < 0.005$).

Thus, cation transport in MDCK cells is unaffected by the expression of THP, but reduced by the process of transfection. The possibility that the process of transfection itself may cause alterations in transport should be considered in evaluating transport in transfected cell lines.

103. Magnesium Depletion Increases NaK2Cl Cotransport in Medullary Thick Ascending Limb (mTAL) Cells. D. Kaji, J. Goyzueta and J. Diaz. Renal Division, Department of Medicine, VA Medical Center, Bronx, NY and Mount Sinai School of Medicine, New York, NY.

The majority of salt reabsorption at the apical surface of mTAL is mediated by the NaK2Cl cotransport. The mTAL is also an important site for Mg reabsorption. While intracellular free Mg concentration is known to modulate NaK2Cl cotransport in other tissues, the effect of varying $[Mg]_i$ on cation transport has not been evaluated in the mTAL.

We depleted $[Mg]_i$ in cells cultured from mouse mTAL by incubation in low Mg media (Mg 0.1 vs 0.6 mM for control media) for 18 h. $[Mg]_i$ measured with FURAPTRA (Mg-Fura 2) was 0.55 ± 0.12 mM in control cells and 0.27 ± 0.09 mM in Mg depleted cells (n = 8, $p < 0.001$ by paired t test). Activities of Na-K pump and NaK2Cl cotransport were measured as ouabain sensitive and bumetanide sensitive (BS) K influx respectively with ^{86}Rb in media containing 145 mM NaCl, 5 mM KCl, glucose 5 mM, pH 7.4 at 37°C, with and without ouabain (3 mM) and bumetanide (10 μM).

Ouabain sensitive K influx was not diminished in Mg depleted cells. However, BS K influx was 42% higher in Mg depleted cells compared to control cells (10.82 ± 1.42 vs. 7.55 ± 1.19, n = 9, $p < 0.001$). Affinity of NaK2Cl cotransporter for external Na, K and Cl was not different in Mg depleted cells. To examine whether the increase in BS ion transport was associated with a similar increase in the number of functioning cotransport sites, we measured ^{3}[H] bumetanide binding. ^{3}[H] bumetanide binding was not increased in Mg depleted cells compared to controls (0.49 ± 0.11 vs. 0.62 ± 0.12 pmol · mg^{-1}).

We conclude that in contrast to erythrocytes, where Mg depletion leads to a decrease in cotransport, Mg depletion in mTAL cells leads to an increase in activity of NaK2Cl cotransport, as measured by BS K influx. The increase in BS ion flux appears to be due to an increase in turnover per transporter site, and not due to an increase in the number of transporter sites.

104. Urea Acutely Inhibits NaK2Cl Cotransport in Mouse Medullary Thick Ascending Limb (mTAL) Cells. D. Kaji and J. C. Parker. Renal Division, Department of Medicine, VA Medical Center, Bronx, NY and Mount Sinai School of Medicine, New York, NY; and University of North Carolina, Chapel Hill, NC.

Acute changes in medullary urea concentrations occur constantly with the state of hydration and protein intake, but the effects of this change on NaK2Cl cotransport have not been evaluated. Subdenaturing, physiological urea concentrations may perturb protein structure, and result in less macromolecular crowding, so that the cells behave as if they are swollen, even at normal cell volume. Because cell swelling decreases NaK2Cl cotransport in many cells, we examined whether urea had any effect on NaK2Cl cotransport in mTAL cells.

NaK2Cl cotransport was measured in cultured mouse mTAL cells as the fraction of K (^{86}Rb) influx that was sensitive to 10 μM bumetanide.

NaK2Cl cotransport was markedly and progressively inhibited by urea in a concentration dependent fashion, with 15% inhibition at 0.1 M urea and almost 80% inhibition with 0.5 M urea ($p < 0.01$ vs control for all urea concentrations). These effects were completely reversible and also observed with two other amides, acetamide and formamide. Urea also inhibited NaK2Cl cotransport measured as Cl dependent or Na dependent K influx. Cell water content, measured with ^{14}[C] 3-O-D-methyl glucose was not different in urea treated cells compared to control cells (3.61 ± 0.32 vs. 3.99 ± 0.32 μl/mg protein). Addition of 0.9 μM okadaic acid or 10 nM calyculin, specific inhibitors of protein phosphatase 1 or 2A, prior to urea, blocked the inhibitory action of urea on cotransport, suggesting that urea acts at a point before the phosphorylation step.

Thus, increased urea concentrations may perturb protein structure, reduce the crowding effect of cytosolic proteins and by this mechanism cause a net dephosporylation of the cotransport protein or some key regulatory protein that controls NaK2Cl cotransport. Acute increase in urea concentration in the medulla may cause a major inhibition of NaK2Cl cotransport in mTAL.

105. Classical and Channel-Like Urate Transporters in Rabbit Renal Brush Border Membranes. Barbara A. Knorr, Jeanne C. Beck, and Ruth G. Abramson. Division of Nephrology, Mount Sinai School of Medicine, New York, New York.

The precise mechanism by which urate is transported across rabbit renal proximal tubule luminal membranes has not been defined.

To determine whether urate flux across this membrane represents simple diffusion or transport on specific carriers, urate uptake was examined in brush border membrane vesicles that were prepared by a magnesium aggregation technique and then exposed to $CuCl_2$.

Urate uptake was consistently many fold in excess of chemical equilibrium. This concentrative, Na$^+$ independent uptake could not be ascribed to non-specific binding or oxidation of transported urate to allantoin. Uptake was voltage sensitive in that it was stimulated by K^+_{out} + valinomycin (val), reduced in the presence of the permeant anion thiocyanate, and reduced by the protonophore FCCP. The latter suggests that uptake is driven, in part, by an H$^+$ diffusion potential generated by copper's oxidation of SH groups. Consistent with this, dithiothreitol (which prevents oxidation of SH groups) virtually obliterated urate uptake. Uptake was cis inhibited by oxonate and trans stimulated by urate. The cis inhibition was not due to dissipation of the P.D. since oxonate did not alter the P.D. generated by K^+_{out} + val (measured with the fluorescent, P.D. sensitive probe diS-C$_3$-(5)). Trans stimulation was evident even when the P.D. was short-circuited with FCCP or "clamped" at a positive P.D. with K^+_{out} + val. Kinetic analysis using the 3–12 sec slopes of uptake revealed saturable and non-saturable components. In paired studies oxonate (0.1 mM) inhibited the non-saturable component: oxonate affected the slope of uptake, not binding.

These studies suggest that there are two mechanisms of urate transport in rabbit brush-border membranes: (1) the demonstration of voltage independent trans-stimulation and saturable uptake provides strong evidence for a classical urate carrier; (2) the demonstration of a non-saturable, but inhibitable component of urate transport indicates that this portion of uptake is not simple diffusion but rather represents facilitated diffusion on a potential sensitive channel-like carrier.

106. Expression of Urate-Anion Exchange in *Xenopus laevis* Oocytes. Barbara A. Knorr, Jeanne C. Beck, and Ruth G. Abramson. Division of Nephrology, Mount Sinai School of Medicine, New York, New York.

One mechanism of urate transport in rat renal proximal tubules is a urate/anion antiporter that exchanges urate for a variety of organic and inorganic ions.

As a first approach to cloning this anion exchanger we have employed the technique of expression cloning in *Xenopus* oocytes. Total RNA was isolated by the method of Chirgwin et al. from rat renal cortex. Poly A$^+$ RNA was selected by oligo-dt-cellulose chromatography. Oocytes were injected with either 50 nl of total poly A$^+$ RNA (50 ng) or H$_2$O. [2-^{14}C]urate uptake was measured on days 2–6 post injection in control and RNA injected oocytes incubated 60 min in ND96 media.

As maximal urate uptake/oocyte/hour was observed on day 3, all subsequent data was obtained at that time point. Urate uptake was stimulated 2–3 fold in RNA injected oocytes compared to those injected with H$_2$O. The stimulated uptake was completely abolished by the disulfonic stilbene DIDS (1 mM), an anion exchange inhibitor. To evaluate the specificity of inhibition, uptake was also measured in the presence of 1 mM oxonate. Oxonate, an inhibitor of a urate transporter that has properties distinct from the anion exchanger, was without effect. To determine the size of the RNA responsible for the stimulation of urate uptake, total cortical poly A$^+$ RNA was fractionated on a 6–20% sucrose gradient. Individual fractions (5) were initially pooled and urate uptake was compared in oocytes injected with 25 ng of each pooled fraction. The 5 individual fractions from the pool that stimulated urate uptake were subsequently injected in oocytes. Urate uptake was maximally stimulated by the fraction containing 1.8 to 2.2 KB poly A$^+$ RNA.

These studies indicate that the oocyte provides a model that permits translation of the RNA of a rat urate transport protein and its insertion into the oocyte membrane. Since the resting membrane potential of the oocyte (−55 mV) would oppose electrogenic urate uptake, and transport is inhibited with DIDS but not oxonate, it is concluded that stimulated transport must be due to translation of the electroneutral urate/anion exchanger. These results indicate that it may be possible to use expression cloning to isolate the cDNA for the urate/anion exchanger.

107. Isolation and Immunolocalization of a Uricase-Like Urate Transport Protein. Barbara A. Knorr, Michael S. Lipkowitz, Barry J. Potter, and Ruth G. Abramson. Divisions of Nephrology and Liver Diseases, Mount Sinai School of Medicine, New York.

Two modalities of urate transport have been reported in rat kidney, a urate/anion exchanger and a potential sensitive, uricase-like uniporter. As an initial attempt to isolate and characterize the responsible transport protein(s), rat renal cortical membranes were harvested, solubilized, and subjected to affinity chromatography with urate or xanthine as the affinity ligand.

Bound protein was eluted with hypoxanthine. Pig liver peroxisomal uricase was purified with the same system and the enzymatically active purified protein was used to generate polyclonal antibodies in rabbit.

In 6 of 10 studies the affinity purified renal protein oxidized urate (following hypoxanthine removal): the specific activity was enriched about 1000 fold compared to solubilized membranes. Silver stain of SDS PAGE gels of the purified protein fraction revealed only 4 protein bands at 27, 32, 36, and 41 kD. Western blot of the purified protein fraction with anti-uricase demonstrated immunoreactive bands at 32 and 36 kD. Immunocytochemical studies of rat renal cortex with the same antibody indicated that the immunoreactivity was localized to the brush-border and subapical sites of proximal tubules. Finally, the antibody to pig liver peroxisomal uricase produced a dose dependent inhibition of urate uptake in renal cortical membrane vesicles (90% at 1 ug IgG/ug membrane protein), but did not alter Na-dependent glucose transport.

These studies demonstrate that the renal cortical plasma membranes contain urate binding proteins which have some functional and immunological homology to the hepatic peroxisomal core protein, uricase. Within the renal cortex, these proteins are localized to proximal tubules, the site of urate transport. Since the antibody which reacts with purified proteins on Western blot selectively inhibits urate transport in intact membrane vesicles it is concluded that at least one of the urate binding proteins is the uricase-like uniporter. It remains to be established whether the 2 non-immunoreactive purified proteins reflect epitopes of this transporter that are not recognized by the antibody or monomers of a different protein, the urate/anion exchanger.

108. Reconstitution of Hepatic Uricase in Planar Lipid Bilayer Reveals a Functional Anion Channel. Edgar Leal-Pinto, Roger D. London, Barbara A. Knorr, and Ruth G. Abramson. Division of Nephrology, Mount Sinai School of Medicine.

Two mechanisms of urate transport have been detected in renal proximal tubule cells: an electroneutral urate/anion exchanger and a urate uniporter that is sensitive to the transmembrane electrical potential. The protein responsible for renal membrane electrogenic urate transport has a number of properties which indicates that it has some functional and immunologic homology with uricase, a protein that resides within the core of liver but not renal peroxisomes. Although uricase functions as an oxidative enzyme in hepatocytes, we have demonstrated that it can also function as a transport protein for urate when inserted into the lipid bilayer of liposomes.

To further characterize the mechanism by which this protein transports urate, uricase was reconstituted in phosphatidylcholine proteoliposomes and then evaluated in planar lipid bilayers. Bilayers were prepared with phosphatidylethanolamine, phosphatidylcholine and cholesterol in a ratio of 16:3:1.

In the absence of uricase, no current was generated when the voltage was ramped between −100 and +100 mV in symmetrical solutions of 220 mM KCl, 2.5 mM urate, pH 7.4 on the cis and trans sides of the bilayer. Insertion of uricase into the bilayer resulted in channel activity as evidenced by clear transitions between open and closed states. The mean unitary slope conductance estimated by the analysis of single channel records was 10 ± 1.0 pS. The current was voltage independent and the channel displayed a high open probability (approximating 50%) with a mean open time > 100 msec. The channel did not conduct K, Na, Cl, or gluconate. Magnesium (0.25–1 mM) significantly decreased the open probability and the mean open time. Oxonate, a known inhibitor of the enzymatic and transport activities of uricase, produced a dose dependent inhibition (ion block) of urate transport on the channel. In contrast to the effect of Mg, oxonate's inhibition was characterized by a decrease in current carried by urate without a change in open probability. In symmetrical 2.5 mM oxonate solutions single channel conductance was at least 2 fold greater than in symmetrical urate solutions, indicating that the channel is more selective to oxonate than urate.

These studies demonstrate that the non-membrane liver peroxisomal protein uricase can behave as a highly selective anion channel when inserted in a lipid bilayer. The ability of this protein to function as a channel suggests the possibility that the renal proximal tubule uricase-like protein transports urate electrogenically because it also functions as an organic anion channel.

109. Regulation of Cystic Fibrosis Gene Expression in Renal Proximal Tubule Cells by Parathyroid Hormone. Michael S. Lipkowitz. Nephrology Division, Mount Sinai School of Medicine.

We have demonstrated that chronic changes in hormones that act via the cAMP/protein kinase A messenger pathway modulate proximal tubule Cl^- permeability. In renal failure in rat, a state in which a variety of hormones are chronically elevated, renal cortical homogenate cAMP levels are elevated and accompanied by a selective increase in brush border membrane Cl^- permeability. Additionally, a chronic infusion of parathyroid hormone, a hormone that is present in excess in uremia and has been implicated as an important uremic toxin, also results in a selective increase in Cl^- permeability.

The cystic fibrosis gene product (CFTR) is a cAMP/protein kinase A regulated chloride channel that is present in renal proximal tubule brush border membranes. Studies were performed after a 3 day infusion of parathyroid hormone to assess whether an alteration in the expression (number) of CFTR channels is involved in the effects of hyperparathyroidism on Cl^- permeability. Immunoblots using an antibody to a peptide fragment of CFTR detect a 165 kD band consistent with CFTR. This band is decreased by 25–30% in renal cortical brush border membrane vesicles from hyperparathyroid compared to control animals.

To begin to assess the mechanism by which CFTR protein expression is regulated, studies were performed to quantitate renal cortical CFTR mRNA. Because of the paucity of CFTR mRNA in renal tissue, reagents were generated to allow quantitation by competitive PCR. PCR is performed simultaneously on sample and standard (CFTR DNA with a new EcoRI restriction site) in the same tube; competition for primers and reagents results in generation of products that reflect the ratio of standard to sample. Subsequent digestion with EcoRI distinguishes sample (uncut, 270 bases) from standard (190 and 80 bases). In studies employing first strand cDNA reverse transcribed from RNA isolated from paired control and parathyroid hormone treated animals, PTH induced a 23% decrease in CFTR mRNA.

Previous studies have demonstrated regulation of CFTR expression in colon carcinoma cell lines; the current studies are the first data that suggest that cystic fibrosis gene expression can be regulated by physiologic stimuli in vivo. Since the decrement in CFTR mRNA is approximately the same as that in CFTR protein, these data suggest that CFTR expression may be regulated at the level of transcription by parathyroid hormone. This decrease in expression (number) of CFTR Cl^- channels may be a counter-regulatory response aimed at preserving cell membrane potential and intracellular electrolyte concentrations in the face of the increased Cl^- permeability (channel activity) induced by PTH.

110. Regulation of Red Blood Cell Chloride Permeability Is Dependent upon Normal Function of the Cystic Fibrosis Gene Product CFTR. Michael S. Lipkowitz and Roger D. London. Division of Nephrology, Mount Sinai School of Medicine, NY.

We have previously demonstrated that human red blood cell membrane chloride permeability is hormonally regulated via the adenylate cyclase/cAMP/protein kinase A messenger pathway. Increases in red cell cAMP induced by epinephrine and norepinephrine resulted in a significant increase in the permeability of chloride relative to that of potassium (PCl/PK). Direct activation of red blood cell adenylate cyclase by forskolin markedly increased intracellular cAMP concentration, and also significantly increased PCl/PK. Finally, in renal failure, a pathological state in which norepinephrine and epinephrine levels are elevated, red blood cell cAMP and PCl/PK are elevated; both cAMP concentration and PCl/PK are normalized by correction of renal failure with dialysis.

Since the cystic fibrosis gene product (CFTR) is a PKA activated chloride channel (or chloride channel regulator) that is present in many tissues, studies were performed to determine whether this protein could be responsible for the regulation of RBC chloride permeability.

Red blood cell membranes were solubilized in SDS, de-lipidated by methanol/chloroform extraction, and separated by SDS-PAGE. Immunoblots using a rabbit polyclonal primary anti-CFTR antibody with detection by a peroxidase-linked secondary antibody and enhanced chemiluminescence demonstrated the presence of a 165 kD band consistent with CFTR.

Red blood cells from patients with cystic fibrosis were incubated for 30 min with or without 10 uM forskolin, after which cAMP was quantitated with an isotopic technique and PCl/PK was determined with the fluorescent, potential sensitive dye diS-C_3-(5). Forskolin produced a marked increase in red cell cAMP (from 44.5 ± 20 to 160 ± 38 pmol/ml cells). Despite this increase in cAMP, forskolin did not produce a significant increment from baseline in PCl/PK (10 ± 6%) in cystic fibrosis patients as opposed to a clear increment in PCl/PK in controls (94 ± 6%).

These studies suggest that the cAMP induced increase in red blood cell membrane PCl/PK is dependent on normal function of the cystic fibrosis gene product, CFTR. Regulation of chloride channel activity has been demonstrated to play an important role in maintenance of cell volume and in the normal function of intracellular organelles in a variety of tissues. The significance of regulation of chloride channels in mature red blood cells remains to be clarified; however, such regulation may play an important role in maintaining homeostasis in the more metabolically active red cell precursors.

111. Chronic Renal Failure Reduces P-Glycoprotein Expression in Rat Brush Border Membranes. Roger D. London, Edgar Leal-Pinto, and Shih Chang. Division of Nephrology, Mount Sinai School of Medicine, New York.

The human multidrug resistance (MDR) gene product, P-glycoprotein actively transports cytotoxic drugs out of cells. Cytotoxic drugs and acute environmental stresses such as heat shock and arsenite can induce P-glycoprotein expression. (In addition expression of P-glycoprotein has recently been associated with a cell volume-regulated chloride channel.) In the present study, the expression of P-glycoprotein was examined in a rat renal ablation model of chronic renal failure.

Kidneys were harvested from control, uni-nephrectomized and 75% nephrectomized rats that were pair-fed for 2–3 months after surgery. Renal cortical brush border membrane vesicles were prepared by isolation on a 15% percoll gradient. P-glycoprotein expression was evaluated by Western blots of brush border membranes and cortical homogenates using C219 monoclonal antibody. Levels of P-glycoprotein expression were quantitated using laser densitometry. Expression of villin, a marker of brush border membrane was also evaluated.

We have previously determined that 75% nephrectomy reduces glomerular filtration rate to approximately one third of control values. In five groups of control and renal failure animals there was a significant reduction (46%, $p < 0.03$) in the expression of P-glycoprotein in brush border of renal failure animals, while the amount of P-glycoprotein in the control and renal failure cortical homogenates was not significantly changed. In contrast, expression of villin was not altered by chronic renal failure. P-glycoprotein and villin expression were not altered by the hypertrophy associated with uni-nephrectomy.

In view of the ability of certain substrates to inhibit their own transport on P-glycoprotein, it is suggested that in chronic renal failure the reduced amount of P-glycoprotein in renal brush border membranes detected in the present study would further reduce the excretion of cytotoxic drugs and/or cyclosporine. Thus reduced renal transport and systemic accumulation of the substrates for P-glycoprotein could synergistically enhance their toxicity in chronic renal failure.

112. Ion Channels in Renal Failure. Roger D. London, Michael S. Lipkowitz, and Edgar Leal-Pinto. Division of Nephrology, Mount Sinai School of Med., New York.

Studies from our laboratory have reported an increase in the ionic permeability of chloride relative to that of potassium (PCl/PK) in red blood cell ghosts of uremic humans and in renal cortical brush border membranes and RBC membranes prepared from rats in renal failure. These observations suggest that membrane ionic permeability is perturbed in renal failure in both polarized and non-polarized cells. In both human and rat membranes, the alteration in membrane permeability was consistently associated with an increase in intracellular concentrations of cAMP in red blood cells and renal cortical homogenates. Since the level of a variety of hormones (PTH, norepinephrine, glucagon, and ADH) that act via the cAMP pathway are increased in renal failure, and cAMP, PKA, PKC and G proteins have been implicated in regulating ion channels, it seemed possible that a cause and effect relationship might exist between the increased PCl/PK and [cAMP] in renal failure. To evaluate whether the open probability and/or number of chloride channels was increased in chronic renal failure, we directly characterized the individual ion channels and examined their regulation.

In preliminary studies, rat BBMV isolated on a 15% percoll gradient were reconstituted in planar lipid bilayers. In symmetrical 150 mM Cesium or TEA chloride, small 7–10 pS channels were observed. These channels were non-rectifying, selective for chloride over cations and inhibited by the chloride channel blocker DPC. Furthermore, addition of protein kinase A (150 units) with 1 mm ATP increased the open probability of channels from normal rat BBMV. Of note, two chloride channel proteins, P-glycoprotein and the cystic fibrosis transmembrane conductance regulator (CFTR) have been localized to the BBMV of renal proximal tubules, and there is evidence that their regulation is, at least in part, due to protein kinase A phosphorylation.

Thus, further studies were performed to evaluate whether the increase in relative ionic chloride permeability is secondary to an increased number of chloride channels in renal failure. When P-glycoprotein and CFTR expression were evaluated by Western blotting, levels of both P-glycoprotein and CFTR were decreased in renal failure brush border membranes, while villin, a marker of brush border membrane was not changed. There was no detectable change in renal cortical homogenates for P-glycoprotein, CFTR or villin. These studies suggest that the amount of two chloride channel proteins is decreased in renal failure. Thus, if the increased PCl/PK is a result of an increase in chloride conductance, and not a fall in potassium conductance, the increased chloride current would be mediated by fewer channels with an increased open probability. Since hormonally induced chronic elevation of [cAMP] would phosphorylate chloride channels increasing their open probability, an adaptive decrease in channel number would act to restore membrane potential towards normal and preserve the transport functions of the renal brush border.

Oncology/Neoplastics

113. Human Tumor Sensitivity Testing Finds New Treatment Options. H. W. Bruckner,[1] P. A. Andreotti,[2] I. A. Cree,[3] K. Becker,[4] P. A. Caruso[2] and I. Gleiberman.[2] [1]Mount Sinai School of Medicine, N.Y.; [2]Batle LE Division, Ft. Lauderdale, Fl; [3]Dundee University, Dundee, Scotland; and [4]Eppendorf University, Hamburg, Germany.

An ATP bioluminescence chemosensitivity assay system evaluated dissociated tumor cells cultured for 5–7 days with proprietary medium in microplates. The assay tests 8 drugs or combinations at 7 concentrations in triplicate using as few as 20,000–40,000 cells obtained by surgery or needle biopsy. The system finds heterogeneity of chemosensitivity between tumors as well as additive or synergistic drug effects. It provides supporting insight into some options for current treatment of ovarian cancer (cisplatin-based), breast cancer (adriamycin-based), and AML (mitoxantrone-based).

Initial results with ovarian, breast, and AML specimens indicate a predictive accuracy of $>70\%$ for sensitivity and $>95\%$ for resistance. Studies with 300 specimens have demonstrated the important role of correlations with clinical experience in order to define optimum *in vitro* assay conditions and criteria for definitions of sensitivity and resistance for each class of tumor.

The system appears to have application for both drug development and selection of regional and combination therapy. The *in vitro* experience with mesothelioma human cell lines carried in nude mice confirmed all known *in vivo* sensitivities and resistances as well as the relative effectiveness of treatment options. Taxol was identified as a promising new drug for mesothelioma. Taxol-Adriamycin combinations were confirmed to be particularly active and an encouraging clinical lead for investigation of both ovarian cancer and mesothelioma.

114. Polypeptide Markers in Pancreatic Cancer. H. W. Bruckner, M. R. Chesser, J. DiGiovanni, L. Farber, J. Mandeli. The Derald Ruttenberg Cancer Center & Department Biomathematics, The Mount Sinai Medical Center, N.Y.

Patients with duct cell pancreatic cancers have greater than normal concentrations of polypeptides (gastrin, substance P, chromogranin, pancreatic polypeptide neurotensin, and gastrin release peptide) in their peripheral blood. (Bruckner et al. AACR 92,93). One-third of patients have a peptide in abnormally high concentrations. GRP is present in 50% of patients with stage IV disease but only $<5\%$ of those with regional disease. Substance P appears to have an association with superior survival, the median approaching 28 and 18 months in patients with stage III and IV disease respectively. Although gastrin is a growth factor, unexpectedly it continues to have an association with superior survival, the median approaching 24 months and 13 months in patients with stage III and IV disease respectively. Chromogranin and pancreatic polypeptide are not associated with good survival. One sixth had 2 peptides in abnormally high concentrations.

Polypeptide production may represent experiments of nature offering insight into physiologic control of pancreatic tumors. Their presence in abnormal concentration is not conclusive evidence that the physician has discovered an endocrine tumor.

115. Triple Biochemical Modulation for Metastatic Adenocarcinoma of the Stomach. H. W. Bruckner, J. Morris, A. Jennis, A. M. Gattani, J. Mandeli, D. Lehrer and M. R. Chesser. Mount Sinai School of Medicine, The Derald Ruttenberg Cancer Center, N.Y.

This regimen, MLP-F, utilizes methotrexate (M), leucovorin (L), and cisplatin (P) in order to modulate bolus and infusional fluorouracil (F). The MLP-F regimen has been described as producing high rates of response and median survival in excess of 1 year for patients (pts) with metastatic adenocarcinomas of the stomach and pancreas (Bruckner et al., Clin Gastroenterol, 1991; and Gattani et al., ASCO, 1992).

Forty-one consecutive eligible pts with adenocarcinoma of the stomach and lower esophagus were given MLP-F. Patient characteristics: All pts had either unresectable disease or residual disease following palliative surgery. All pts had a performance status of 0–2. Median age was 60 years, but 13 pts were less than 50 years old. Thirty pts were males. Palliative resection was performed for 15; 17 had no surgery; and 9 were explored only. Thirty-four pts were given MLP-F as initial treatment.

Overall median survival for this treatment group was 15.8 months. Overall response rate was 59%. The complete response rate was 27%. Thirty percent of all pts survived more than 2 years. Three of the 34 pts discontinued MLP-F electively and subsequently progressed, and 7 additional pts were treated with MLP-F after receiving other prior chemotherapy. The response rate in these 10 pts who had received prior chemotherapy was 60%. Median survival from start of MLP-F for pts with prior chemotherapy was 9.7 months.

Unlike experience with other chemotherapy, peritoneal disease does not override the impact of MLP-F therapy. When the patient's survival was examined, based on a published survival model which employed nine objective prognostic laboratory tests (such as albumin, bilirubin, CEA, white blood count), even the pts with poor prognostic features achieved a median survival approximating 1 year; this survival is better than that of the historical group with good prognostic characteristics.

116. Tumor Markers Provide Objective Prognostic Information in the Context of Combined Modality Pancreatic Cancer Trials. A. M. Gattani, J. Mandeli, and H. W. Bruckner. Mount Sinai School of Medicine, The Derald Ruttenberg Cancer Center, New York, N.Y.

Patients with stage II–III pancreatic cancer (PC) were treated with regimens using combined modality methods (Bruckner et al., AACR '89 and Kamthan et al., ASCO '92) and biochemical modulation (Gattani et al., ASCO '92; Bruckner et al., J Clin Gastroenterol '91 and Cancer Res '88). Pretreatment tumor markers, carcinoembryonic antigen (CEA), CA 19-9, and CA-125 (Dianon Laboratories) were evaluated regarding their correlation with survival in 34 patients.

Analyses revealed naturally occurring gaps in the distribution of assay values. This gap divided patients into "good" vs. "bad" risk groups. A CA 19-9 assay of 2,000 u/ml divided patients into two groups; 23 'low assay' patients ($<2{,}000$) had a median survival time (MST) of 17.9 months (mos), 11 'high assay' patients ($\geqslant 2{,}000$) had a 7.4 mos MST, (p.0002). A CEA assay of <10 mg/ml identified 28 patients as a low assay group, 17.9 mos MST, and 6 patients as a high assay ($\geqslant 10$ mg/ml) group with MST of 6.1 mos (p.001). Simultaneous assays for example, CA 19-9 plus CEA low assays found 19 "good" prognosis patients with a MST of 22.8 mos (p.0002). CA 19-9 and CA 125 high assays found 6 "poor" prognosis patients with MST of 6.8 mos (p.0001).

Conclusions. The assays assigned the majority of patients to good risk groups. The MST exceeded that found using any published prognostic test for similar unresectable stage II–III PC. The "bad" risk group has an equal or better survival compared to historical patients overall. These methods of prognostication contradict the normal expectations for a majority of patients and identify a high priority group for treatment. These results warrant the use of baseline tumor markers in the design (stratification) and analysis of clinical trials for the treatment of pancreatic cancer. That the majority of patients achieve a survival of heretofore unexpected length implies that the combined modality treatment may contribute favorably to the survival of patients.

117. High Dose Zidovudine (AZT) in Patients with Treated Myelodysplastic Syndromes (MDS), and Relapsed or Refractory Acute Leukemia. L. R. Silverman, J. Roboz, E. P. Demakos and J. F. Holland. The Derald H. Ruttenberg Cancer Center and The Department of Neoplastic Diseases, Mount Sinai School of Medicine, New York, NY 10029.

AZT, a chain terminator of DNA synthesis with myelosuppressive effects in patients with AIDS, can inhibit the growth and induce the differentiation of HL-60 leukemia cells in vitro.

AZT was administered po q6h in divided doses rounded off to the nearest 100 mg, according to diagnosis and preset cohorts (MSSM GCO #89-306 NPD*): 900 mg/m^2/d (n = 3); 1100 (n = 5); 1300 (n = 1); 1500 (n = 4); 1700 (n = 3). Doses were escalated in 3 patients. Ten of 11 patients diagnosed with MDS (2), transformed (tx) AML following MDS (2), tx biphenotypic leukemia following MDS (3), refractory AML (1) relapsed biphenotypic AML (1) and secondary AML (2) were evaluable. All patients had failed at least one prior treatment regimen (median 2). The median age was 63 (22–76); 5 were male and 5 had a PS 0-1.

Responses occurred in 5; 1 CR (MDS); 2 PR (tx AML, biphenotypic AML); 2 Improved (2 tx AML). Marrow aplasia did not occur in any patient. Grade 4 leucopenia occurred in one patient and thrombocytopenia occurred in three. Increased skin pigmentation was seen in four patients. Pharmacokinetic studies by HPLC demonstrated peak AZT serum levels between 4.3–16.4 μM and AZT glucuronide peak levels between 8.6–48.8 μM.

No correlation of dose and hematologic effect has yet been established. Peak levels (30′–90′) tended to increase within single patients as doses escalated. Absolute doses of AZT ranged from 1200–3600 mg/day up to 7× higher than the dose in AIDS. High dose AZT was well tolerated and produced clinical responses, without bone marrow aplasia, in a heavily pretreated group of patients with advanced myelodysplasia and derivative leukemias.

Pulmonary

118. Pyrazinamide-Induced Hepatic Necrosis Treated with Liver Transplant. J. J. Adler, B. Meyers, C. Miller, F. Klion. Departments of Medicine and Surgery, Mount Sinai Medical Center, N.Y.

While pyrazinamide (PZA) is a recognized cause of drug-induced hepatitis, hepatic necrosis remains a rare complication of this drug. In the early years of TB chemotherapy PZA was relegated to "second line" status in part because of its hepatic toxicity when compared to other drugs. In recent years PZA has been used as "first line" treatment because of its specific tuberculocidal effect on intracellular organisms and its efficacy in short course treatment regimens. With the increased frequency of multiple-drug-resistant tuberculosis (MDR TB), greater use of PZA for both the treatment of active disease and preventive therapy in individuals thought to be infected with MDR TB is anticipated.

A 30-year-old black woman whose husband had documented MDR TB with an organism resistant to isoniazid (INH), rifampin, streptomycin, and ethambutol, along with her 2-year-old daughter converted their tuberculin skin tests. Initially, the patient took INH preventive therapy, but when the drug resistance pattern became known, she was placed on PZA (20 mg/kg) and ofloxacin (800 mg) and INH was discontinued. Laboratory studies showed elevation of ALT and GGT 3 times baseline prior to the discontinuation of INH. Three weeks after starting PZA the patient noted nausea, vomiting, scleral icterus, and dark urine; she stopped all medication immediately. However, over the next ten days she developed progressive hepatic failure, necessitating emergency liver transplant.

This person in close contact with a patient with MDR TB is highly instructive in pointing out the risk of hepatic necrosis with indicated therapy for MDR TB. In addition, with the need for prolonged immunosuppressive treatment, the scope of tuberculosis prevention in liver transplant patients with both sensitive and multiple resistant organisms will increase.

119. Transbronchial Biopsy (TBB) Significantly Enhances Yield of Bronchoscopy in HIV-Infected Patients; 1992. L. Bernstein, S. Salzman, P. Villamena, M. Rosen. Division of Pulmonary and Critical Care Medicine, Beth Israel Medical Center (BIMC), N.Y.

Fiberoptic bronchoscopy (FOB) techniques used to diagnose HIV-related pulmonary disorders vary by institution. The high frequency of *P. carinii* pneumonia (PCP) and the high sensitivity of bronchoalveolar lavage (BAL) in diagnosing PCP has led to BAL use alone during FOB. PCP prophylaxis and sputum induction have reduced the number of cases requiring FOB and may alter FOB yield.

To evaluate TBB and BAL yield, we reviewed the records of all patients who had FOB at BIMC in 1992. Of 519 FOBs performed, 205 were in 182 known or suspected HIV-infected patients.

37 cases were nondiagnostic, 180 diagnoses were established and 13 patients had dual diagnoses as shown below:

Diagnosis	N (%)	BAL smear*	TBB path*	TBB+/BAL−†
PCP	105 (58)	90/105 (86%)	85/99 (86)	15/106 (14)
KS (13/15 visual)	15 (8)	—	4/10 (40)	2/15 (13)
Bacterial pneum.	15 (8)	—	4/15 (27)	4/15 (27)
CMV	12 (7)	4/12 (33)	11/12 (92)	8/12 (67)
Inter. pneum/Fib.	12 (7)	0/12 (0)	12/12 (100)	12/12 (100)
M. tuberculosis	6 (3)	6/6 (100)	1/5 (20)	0/6 (0)
M. avium comp.	3 (2)	2/3 (67)	0/3 (0)	0/3 (0)
Fungi	5 (3)	3/5 (60)	3/4 (75)	1/5 (20)
Non-KS malign.	5 (3)	3/5 (60)	4/4 (100)	2/5 (40)
Nocardia: 1 Cx+	2 (1)	1/2 (50)	0/2 (0)	0/2 (0)
Total diagnoses	180 (100)	109/150 (73%)	124/166 (75%)	44/180 (24%)

* Specimens positive obtained

† Specimens positive/total diagnosed.

Conclusions. PCP remains the most common disease diagnosed by FOB. Diagnoses were made exclusively by TBB in 24% of cases including 14% of PCP cases. Some disorders resembled PCP clinically, but were only diagnosed by TBB. When performing FOB in HIV-infected patients, TBB significantly enhances diagnostic yield over BAL alone.

120. Connexin43 Expression Regulates Growth in Cultured Human Airway Smooth Muscle Cells (HASM): 1992–93. Louis R. DePalo. Division of Pulmonary Medicine, Mount Sinai Hospital, NY.

Direct intercellular communication via gap junctions is an important mechanism allowing the coordination of tissue function on a cellular level. Gap junctions are formed by the apposition of cell membranes containing hexameric assemblages of structural proteins termed connexins. The intercellular exchange of second messenger molecules and ions between coupled cells may amplify the effects of localized nervous or humoral stimulation on synchronized tissues, and perhaps synchronize metabolic as well as electrical activity in the tissue. This exchange of cellular information is used to coordinate diverse cellular functions such as pattern formation in development, electrotonic coupling in the nervous system and smooth muscle viscera and specific tissue responses to injury (liver). Recently, it has been shown that the lack of formation of functional gap junctions in human carcinoma can be correlated to metastatic potential, suggesting that the gap junction may be an important regulator of cellular growth and contact inhibition.

We have previously shown that cultured tracheal myocytes express a human homologue of rat connexin43, the major gap junctional protein in heart and vascular tissues. Expression of connexin43 in this tissue results in dye- and electronic coupling with a mean junctional conductance of 9.43 ± 1.01 nS (SEM, N = 41) and unitary conductance of about 90 pS. Inhibition of connexin43 expression by antisense oligonucleotides (Cx-AS) significantly inhibited both dye coupling and levels of connexin43 detectable by immunoblot (0.59% ± 0.09 SD). Junctional conductance (gj) was greatly inhibited by Cx-AS [(17.75 ± 3.0 (SE), N = 4) vs. 4.39 ± 3.06, N = 9) ($P \leq .05$, Students t-test)].

HASM cells grow to confluence in response to PDGF and demonstrate significant contact inhibition with a flattening of the growth curve and marked diminution in bromodeoxyuridine incorporation. Cell cycling at confluence constitutes approximately 1–4% of the cell population. Addition of 100 μM Cx-AS resulted in a significant increase in cell number of approximately 0.20% ± 0.005 (N = 4) in response to serum and evidence of an increase in S phase cycling as determined by incorporation of BUDR over controls treated with a nonsense oligonucleotide. In contrast, Cx-AS addition to confluent rat aortic smooth muscle (RASM) cells (expressing connexin43 without significant dye coupling or significant contact inhibition) showed no difference in cell counts compared to non-sense treated controls.

Cultured HASM express connexin43 and form functional gap junctions. Connexin43 expression and functional gap junction formation can be significantly inhibited by the addition of antisense oligonucleotides to the connexin43 gene. Inhibition of gap junction formation in confluent cultures results in loss of contact inhibition with resultant cell cycle entry and cellular proliferation. Smooth muscle hyperplasia in airway disease may thus be regulated in part by gap junctions. Cx43 antisense inhibition, however, fails to result in proliferation of RASM, cells that express connexin43 without tight functional coupling and that lack significant contact inhibition. The precise role of gap junction formation and intercellular coupling in regulating proliferation in different tissues deserves further study.

121. The Effect of High Dose Steroids on Sleep Patterns and Respiratory Function in Symptomatic Steroid-Dependent Asthmatics. Fein E, Godbold J, Chusid E, Schachter EN. Mount Sinai School of Medicine New York, NY 10029.

Nocturnal and early morning wheezing is common among asthmatics, yet the mechanism and therapeutic approach are unclear. Some studies indicate a correlation between the severity of asthma to these symptoms and the frequency of nocturnal awakenings.

We recruited ten adult steroid dependent asthmatics on a stable (at least three months) dose of the equivalent of prednisone ⩾7.5 mg but ⩽20 mg. Following Albuterol, all subjects demonstrated improvement of lung function of at least 15% of the FEV_1. All patients signed informed consent approved by our Institutional Review Board. Each patient was studied for a four week period. During the first two weeks, the patients were followed on their standard medications. During the second two week period, patients were placed on 40 mg of oral prednisone while continuing their usual bronchodilator therapy. Subjects were provided with a questionnaire and were asked to record the number of times they were awakened due to their asthma during the previous night. Additionally, they reported the severity of symptoms (scale 0–3) for wheeze, dyspnea, and cough and overall symptoms (scale 0–4). They also recorded the number of puffs of bronchodilator and theophylline tablets used during the previous twenty-four hour period. Finally peak flow rates were measured in the morning and in the evening. There were 6 female and 4 male asthmatics studied, aged 22–66.

The baseline lung function of our subjects was: FVC 90% ± 13%, and FEV_1 63% ± 12% expressed as a percent of predicted. The mean dose of prednisone on entry to our study was 12.5 mg. ± 3.35. The mean number of awakenings during the second week of the study was 0.7 ± 0.3, and 0.20 ± 0.05 during the fourth week of the study ($p = 0.0001$). A trend of increasing AM and PM peak flows were noted for the group during weeks three and four. Whereas the mean scores for wheeze, dyspnea, overall symptom score, puffs of bronchodilator, cough, and number of theophylline tablets per day improved significantly when comparing week two to four.

We conclude that stable symptomatic steroid dependent asthmatics suffer frequent nocturnal awakenings. Increased corticosteroid dosages in such individuals rapidly decrease the number of awakenings and concurrently improve other respiratory symptoms.

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122. Mucin Gene Expression in an Endometrial Adenocarcinoma Cell Line. E. G. Gollub, S. Goswami, D. Kouba and Z. Marom (SPON: E. Schwartz). Division of Pulmonary and Critical Care Medicine, Mount Sinai Med. Center, New York, N.Y. 10029.

The endometrial adenocarcinoma cell-line (Ishikawa cells) secretes a mucin which resembles airways epithelial mucin. Cells treated with nanomolar amounts of calcium ionophore, A23187, exhibit greatly enhanced mucin secretion.

To examine the regulation of mucin secretion at the molecular level, cells were treated with A23187 and the expression of mucin genes was analyzed by Northern blot hybridization. Five distinct mucin genes have been identified (MUC 1–MUC 5) to date. Synthetic oligonucleotides corresponding to the sequences of MUC 1–MUC 5 were used as hybridization probes.

Only MUC-4, originally isolated from a tracheobronchial cDNA library, hybridized to RNA prepared from control and A23187-treated cells, exhibiting a discrete band slightly below the 28S RNA (~5 kb). The RNA from the stimulated cells gave a 3–4 × higher signal. Treatment of the cells with other secretagogues, hydroxyeicosatetraenoic acid (HETE) and carbachol) also up-regulated the expression of MUC 4.

Thus, enhanced mucin secretion in Ishikawa cells is accompanied by increased levels of MUC-4 mRNA. These results may indicate an effect on (a) RNA transcription, or stability, or (b) in the case of the ionophore, a general effect on mRNA levels related to an increased influx of calcium.

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123. Phosphoinositide Hydrolysis and Protein Kinase C Activation by 15 Hydroxy Eicosatetraenoic Acid Induces Mucin Secretion in an Epithelial Cell Line. S. K. Goswami and Z. Marom. Division of Pulmonary and Critical Care Medicine, Mt. Sinai Hospital, New York.

We have demonstrated previously that 15-hydroxy eicosatetraenoic acid (15-HETE) is a potent mucus secretagogue in human airway explants in culture. We have established an epithelial cell line (Ishikawa cells) which secreted mucin like glycoprotein (MLGP) under a variety of external chemical stimuli.

Since 15-HETE enhances mucin secretion in human airway explants, the present investigation was undertaken to study the effect of 15-HETE on MLGP secretion, if any, in Ishikawa cells and the underlying mechanism(s) involved therein. 15-HETE (2.5 μg–10 μg/ml) induced a dose-dependent increase of MLGP (20 ± 2% to 60 ± 2% increase over control, $n = 4$). It has been demonstrated by us that rise in intracellular Ca^{++} is vital for the secretion of MLGP in these cells. Intracellular Ca^{++} is altered by the generation of inositol triphosphate during phosphoinositide (PI) hydrolysis. We, therefore, studied the effect of 15-HETE on PI hydrolysis in [3H] myo-inositol labeled cells.

PI turnover was increased by 15-HETE in a dose-dependent and time dependent fashion. Protein Kinase C (PKC) activation in these cells by phorbol myristate acetate (PMA) has been shown to enhance MLGP secretion. It is feasible that 15-HETE by generating diacylglycerol during PI hydrolysis could activate PKC and induce MLGP secretion. In order to substantiate this hypothesis, we used (i) a PKC inhibitor, 1-(5 isoquinolinyl sulfonyl)-2-methyl piperazine (H-7), and (ii) down-regulation of PKC by incubating the cells with PMA for 6 hours. In both instances the MLGP secretion by 15 HETE was inhibited.

These findings strongly suggest that 15-HETE exerts its mucus secretagogue activity by the activation of PKC.

Supported by NIH Grant 37254.

124. Phospholipase C Activity in Human Respiratory Smooth Muscle Cell Is Inhibited by Both Protein Kinase A and Protein Kinase C Medicated Phosphorylation. S. K. Goswami and Z. Marom. Division of Pulmonary and Critical Care Medicine, Mount Sinai Hospital, New York.

Human respiratory smooth muscle cell (HRSMC) was isolated from human airways by established methods. Immunohistochemical staining of these cells showed the presence of myosin, smooth muscle actin and desmin. Actin and myosin's smooth muscle origin was further identified by the presence of m-RNA encoding α-actin and smooth muscle myosin light chain by blot hybridization with ^{37}P labeled CDNA probe. Bradykinin (BK) and sodium fluoride (NaF) were used as activators of phospholipase C (PL-C). PL-C activation induces polyphosphoinositide (PI) hydrolysis and generation of myo-inositol phosphates (IPs). [3H] Myo-inositol labeled HRSMC was used to measure IP's production by BK and NaF.

BK (10 ^{4}M to 10 $^{+}$M) enhances PI hydrolysis in a dose-dependent manner. NaF induces the release of IP's in a linear fashion with optimal induction occurring at 25 mM. Both effects were blocked (about 50%) by pre-treatment of cells with forskolin (10 μM), a Protein Kinase A (PKA) activator. Phorbolmyristate acetate (PMA), an activator of Protein Kinase C (PKC), also inhibited PI hydrolysis induced by BK and NaF.

Since the site of activation by NaF is believed to be a GTP binding protein and forskolin inhibits both BK and NaF induced PI hydrolysis it is very tempting to speculate that a GTP binding protein is involved in coupling the BK receptor to PL-C. Forskolin, by activating PKA, could mediate the phosphorylation of this GTP binding protein and inhibit PL-C activity.

Supported by NIH Grant 37254.

125. Isolation and Characterization of a Novel Epithelial Cell-Specific T Lymphocyte Ligand. TH Kalb, M Walter, Y Li, and L Mayer. Divisions of Pulmonary/Critical Care and Clinical Immunology, Mount Sinai Hospital, NY.

Introduction. Airway (AEC) and intestinal (IEC) epithelial cells have been previously shown to stimulate different T lymphocyte populations ($CD4^+$ vs $CD8^+$ respectively) in epithelial driven allogeneic MLR. This stimulation can be blocked in both airway and intestinal stimulators by preincubation of these cells with each of the epithelial-specific mAbs L12, B9 or B39 (generated against IEC). In order to understand the regulation of the molecules recognized by these mAb on AEC and IEC, we utilized cell lines to aid in their characterization.

Method. Immunohistochemical staining was performed on formalin fixed cells (Adherent A549 derived from alveolar epithelium; and intestinal cell lines HT-29 and T-84). Immunoprecipitation of the epithelial antigens recognized by these mAb was performed on ^{125}I surface labelled cell lysates (NP-40 3%/SDS 0.5%), and precipitated with either anti-class I (W6/32), IgG1 isotype control, or B9, L12, B39 mAbs, and resolved on SDS-PAGE. Immunoblots were performed on unlabelled cell lysates transferred to nitrocellulose after SDS-PAGE.

Results. Immunohistochemical staining of A549 revealed intense surface staining for B39. L12 antibody staining was also found and appeared to be upregulated after PMA exposure. Faint staining with B9 mAb was detected, though no modulation was seen. A549 does not express class II MHC by immunohistochemistry (mAb VG2.2), with or without IFN-γ incubation, nor do A549 stimulate in allogeneic MLR. HT-29 also express L12 and B39 epitopes, though no modulation was seen with IFN-γ, LPS, or PMA. ^{125}I Immunoprecipitation of A549 lysates with L12 mAb revealed a 42–44 kD band. No immunoprecipitates have been detected with B9 or B39 mAbs. In HT-29 immunoprecipitates, a L12 band at 45–55 kD was detected, as well as 69 kD B9 and 60 kD B39 bands. On immunoblot of A549 lysate, the L12 antibody detected a 43 kd band, similar to the appearance of a immunoblot prepared from intestinal cell lysate.

Conclusion. Airway and intestinal epithelial cell lines share a 43 Kd surface antigen (L12 Ag) which may be a novel restriction element in cognate interaction between epithelial cells and lymphocytes. This antigen differs from known accessory molecules (including MHC, LFA-1, LFA-3, ICAM-1, 2, and B7/BB1) with regard to tissue distribution and expression, functional characteristics, and immunoblot/immunoprecipitation pattern. Expression of L12 antigen appear necessary but not sufficient for stimulation of AEC driven MLR. Although L12 Ag may be involved in cognate interaction with T lymphocytes, its presence on both AEC and IEC argue against the hypothesis that it is a specific CD8 ligand.

126. Elevated Intra-Abdominal Pressure and Intrinsic PEEP: Common Confounders of Occlusion Pressure Interpretation? Nelson JE, Brown LK, Nierman DM, Kalb TH, Oropello JM. Divisions of Pulmonary and Critical Care Medicine, and Surgical Intensive Care, Mount Sinai Hospital, N.Y.

Interpretation of the pulmonary artery occlusion pressure (PAOP) is complicated by changes in intrapleural pressure (P_{pl}). Two factors potentially raising P_{pl}, elevated intra-abdominal pressure (P_{ab}) and intrinsic PEEP ($PEEP_i$), are of particular concern because they may go unrecognized. The purpose of this study was to assess the prevalence of these factors in patients with pulmonary artery catheters (PAC), and to evaluate their effect on P_{pl}.

Methods. Twenty consecutive MICU patients with PAC were studied during assisted mechanical ventilation. P_{ab} was measured using a transurethral bladder catheter.[1] $PEEP_i$ was measured ($n = 19$) by respiratory inductance plethysmography.[2] P_{pl} was measured ($n = 9$) with a balloon esophageal catheter (CP-100 Monitor, BICORE). All pressures were measured at end-expiration in semi-erect position.

Results. Thirteen of 20 patients had $P_{ab} \geq 10$ mm Hg (range 2–19 mm Hg). Six had $P_{ab} \geq 15$ mm Hg. Four patients with $P_{ab} \geq 10$ had no clinical evidence of GI disease. Fourteen of 19 patients had detectable $PEEP_i$. Five of these had neither clinical evidence of flow limitation nor $\dot{V}_E > 10$ l/min. No patient had $PEEP_i > 8$. Neither $PEEP_i$, P_{ab}, nor their sum was correlated with P_{pl} ($p > 0.05$).

Conclusions. In our sample, $P_{ab} \geq 10$ occurred frequently, suggesting that this is a common but under-recognized clinical entity. $PEEP_i$ was also detectable in many patients, and not restricted to those with obvious airflow limitation or high $\dot{V}_E$, but occurred at modest levels. Our inability to detect a consistent effect of these variables on P_{pl} may reflect the role of such other variables as pulmonary or thoracic compliance, or the relationship between bladder and subdiaphragmatic pressures. Other studies have suggested that both P_{ab} and $PEEP_i$ can affect P_{pl}, and that P_{pl} affects both hemodynamics and PAOP interpretation. Moreover, animal studies predict that $PEEP_i$ would cause even greater increases in pulmonary capillary pressure than in PAOP. Therefore, a clearer understanding of the interrelationship of these variables in the ICU setting is warranted.

GCO # 91-529.

References

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127. Characterization of the Potentiation of Bradykinin-Induced Constriction by an Inhibitor of Endopeptidase 24.15. E. N. Schachter, A. Tsai, C. Cardozo, E. Zuskin, J. Godbold, N. Rienzi, M. Lesser. Mount Sinai Medical Center and the VA Medical Center, New York, New York and the Bronx, USA.

We have previously shown (ARRD 143:A616, 1991) that the blocking of a metallo-endopeptidase (EP24.15), that degrades bradykinin, by cFP-AAY-pAB, enhances the bronchoconstrictor activity of bradykinin in guinea pig trachea (GPT).

To evaluate the role of known modifiers of bronchoconstriction we repeated our experiments under the following conditions: (1) GPT with and without epithelium and (2) GPT in the presence of indomethacin 1 uM. We also studied the effect of the incubation time of GPT with inhibitor, cFP-Ala-Ala-Phe-pAB (I 24.15). Four rings obtained from each animal were initially stimulated with bradykinin 10 uM and again, following treatment (3 minutes before the second challenge with bradykinin) with 1) control solution 2) I 24.15 (10 uM) 3) Thiorphan (T) (10 uM) 4) I 24.15 and Thiorphan. We also studied rings that had been pretreated with indomethacin 1 uM and rings from which the epithelium was removed. Finally we examined rings to which I 24.15 was added 5, 15, 25 and 35 minutes before the second addition of bradykinin.

Table 1 shows the percent increase in contractile response to bradykinin (compared to baseline) after the addition of inhibitor.

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	With epithelium	Without epithelium	Indomethacin pretreatment
Control	+37%	−14%	+97%*
I24.15	+56%*	+25%	+114%*
T	+110%†	+65%	+424%†
T + I 24.15	+149%†	+31%	+219%†

* $p < 0.05$
† $p < 0.01$

The enhancing effect of I 24.15 can be seen in the presence of epithelium but was not seen in its absence. Pretreatment with indomethacin enhanced GPT reactivity to bradykinin in general. Finally enhancement by I 24.15 was seen at 5′ and 15′ following incubation but not at 25′ or 35′.

We conclude that EP24.15 in airway epithelium modulates bradykinin-induced contraction of GPT; this effect is non-specifically enhanced by suppressing prostaglandin synthesis.

128. Comparable Bronchodilator Effects of Albuterol and Ipratropium in Mild Stable Asthma. Spiro P, Rienzi N, Schachter EN. Mount Sinai School of Medicine, New York, NY.

Ipratropium bromide (IB) is an anticholinergic quaternary amine which has known bronchodilator effects in patients with obstructive lung disease. In asthma it is commonly held that β-agonists are more effective as bronchodilators than IB.

We developed a protocol to compare the relative bronchodilatory effects of IB vs Albuterol in patients with stable asthma. We tested 9 subjects with a clinical history of asthma, average age 34.3, (range 21–57), without recent respiratory infection or the use of corticocosteroids in the last 4 weeks. All patients had an established bronchodilator response (ATS criteria, 1991). Patients abstained from the use of bronchodilator medications for at least 12 hours prior to testing. Subjects received either IB (36 μg) via two inhalations, or Albuterol (180 μg) via two inhalations using standard meter dose inhalers. Spirometric measurements were obtained immediately before and ten minutes after inhalation of the bronchodilator.

All patients responded to Albuterol but only 6 of 9 responded to IB. Following Albuterol the following percent increases were noted, FVC: 11.5% ± 7 (mean ± SD), FEV1:23.2% ± 8. Following IB, among the responders, the following percent increases were noted FVC:10.2% ± 9 and for FEV1:24.2% ± 9. Comparison of these two responses by the paired t-test showed no significant differences. We also correlated the responses to Albuterol and IB with the age of the patient and the baseline FEV1 expressed as a percent of predicted and found no significant correlation. ($r = .173$ and $.234$ Albuterol and $r = .563$ and $.471$ for IB)

We conclude that in a small group of stable young asthmatics with a positive response to Albuterol, the response to IB was frequent 66% (6/9). When it occurred, the response to IB was as great as the response to Albuterol at 10 minutes after the delivery of the medication.

Rheumatology

129. An Association between Refractory HELLP Syndrome and Antiphospholoid Antibodies during Pregnancy: a Report of Two Cases. M. Ornstein, J. Rand. Divisions of Rheumatology and Hematology, Mt. Sinai Medical Center, New York, NY 10029.*

The HELLP Syndrome is a thrombotic microangiographic vasculopathy that presents in pregnancy consisting of hemolysis, elevated liver enzymes and low platelets. HELLP usually resolves with delivery of the fetus without sequelae, and often is managed well with conservative care. There have been no prior reports of an association between HELLP and the presence of elevated titers of anticardiolipin antibodies.

We now report two cases of patients who each presented with HELLP Syndrome that was refractory, despite delivery of the fetus, corticosteroids, and anticoagulation. Both patients were found to have elevated levels of anticardiolipin antibodies. Examination of skin and placental pathology revealed diffuse deposition of fibrin with small vessel thrombi, without evidence of vasculitis. Coincident with plasmapheresis, HELLP resolved in both patients.

We conclude that there may be an association between the presence of antiphospholipid antibodies and a protracted HELLP syndrome in pregnancy; this may be a new manifestation of the antiphospholipid syndrome. Plasmapheresis appears to benefit these patients.

130. Scleroderma in Association with Silicone Chin and Toe Implants: a Report of Three Cases. Harry Spiera, Leslie Dubin Kerr. Division of Rheumatology, Mount Sinai Medical Center, New York, NY 10029.

Scleroderma has recently been described in association with the use of silicone-containing breast implants. We report our experience with three scleroderma patients seen in association with the use of silicone implants other than breast implants. Of these three patients, two had the CREST variant of scleroderma and one patient had diffuse scleroderma (PSS). Two patients received silicone-containing chin implants. The third patient received a silicone-containing hinge toe implant. The patient with PSS died secondary to progressive cardiomyopathy despite removal of the implant. The two CREST patients are currently clinically stable with their implants in-situ.

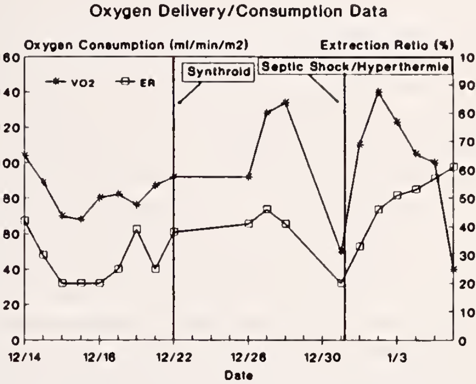
These data extend the previous observations related to silicone breast implants and scleroderma to other silicone-containing prosthetic devices. A history of exposure to any silicone-containing device should be sought by physicians caring for scleroderma patients.

Clinical Abstracts

131. Hypothyroidism, Hypometabolism and Oxygen Consumption/Delivery Dynamics. P. Spiro, D. Nierman. Division of Pulmonary and Critical Care Medicine, Mount Sinai Medical Center, NY.

A case is presented in which invasive measurements of oxygen delivery and consumption may have helped to distinguish true hypothyroidism from the euthyroid sick state.

The patient was an 81-year-old female with HTN and mild OMS transferred from another hospital for rehabilitation. Her previous hospital course included a new diagnosis of Wegeners Granulomatosis. Shortly after transfer she developed a RLL infiltrate on CXR. Despite broad spectrum antibiotics, three days later she became hypotensive and was intubated. Initial MICU evaluation revealed an obese, lethargic woman, Temp$_{core}$ of 33°C, with peripheral edema, sallow skin and coarse hair. A PA catheter revealed a C.I. = 3.3 L/min, SVR = 1500 dynes · sec/cm^5, PCWP = 14 mm Hg, DO_2 = 408 ml/min · m^2, VO_2 = 108 ml/min · m^2, E.R. = .27 and a lactate of 1 mEq/L (Fig). Initial thyroid function tests were consistent with sick euthyroid ($T_4 < 1$ µg/dl, TSH 3.2 µU/ml). Unexpectantly, over the next eight days, despite fluids, PRBCs, dopamine and dobutamine, her VO2 as calculated by the Fick method remained persistently low and fixed and multiple lactates were normal over a wide range of DO_2. On the 10th ICU day, because of persistent hypometabolism, the patient was begun on 0.25 mcgs of synthroid. The normal initial TSH may have been secondary to the exogenous administration of dopamine. The VO2 and ER(O2) progressively improved and she was stable off pressors. TFTs 3 days after starting synthroid revealed a paradoxical rise in TSH. After eight days on synthroid she developed hemodynamics of septic shock and, despite aggressive treatment, died 9 days later.



Post-mortem exam showed a markedly atrophic thyroid gland. Persistent and unexplained hypometabolism may help to differentiate hypothyroidism from ESS.

132. Thyrotropin-Secreting Pituitary Macroadenoma: Endocrine, Biochemical, Morphological Studies, and Therapeutic Approach. M. Alvarez-Marfany, S. Morgello, K. Post, A. C. Levine. Divisions of Endocrinology, Neurosurgery, and Pathology. Mount Sinai Hospital, NY.*

A 40-year-old male with a chief complaint of visual difficulty was referred for evaluation of a pituitary mass. The clinical evaluation was remarkable for visual loss in the right eye, headaches, profuse sweating, heat sensitivity, insomnia, palpitations, and weight loss. Right temporal hemianopsia and a small diffuse goiter were noticed on physical exam. MRI scan showed a very large sella suprasellar mass lesion with eccentric extension towards the right. The ophthalmologic evaluation was consistent with right optic nerve compression. High serum levels of T_4 (23.9 µg/dL) and T_3 (498 ng/dL) associated with a supranormal serum TSH (7.8 µU/mL) were detected. Upper normal serum LH levels (21 mIU/mL) were also noted with normal levels on the remainder of the anterior pituitary hormones.

These findings indicated the presence of hyperthyroidism due to inappropriate secretion of TSH, whose neoplastic origin was clinically evident and documented by imaging studies. The diagnosis was confirmed by elevated α-subunit level (21.1 ng/mL), and α-subunit/TSH molar ratio (24.2). Subsequently a transsphenoidal adenectomy with subtotal removal of the adenoma was performed, followed by radiotherapy for residual tumor. Immunohistochemical staining of the adenomatous tissue removed at surgery was positive for TSH and LH. Following the surgery, TSH levels fell transient, the hyperthyroidism persisted. The patient is presently being treated with propylthiouracil. Somatostatin analog therapy is also being considered.

TSH-secreting pituitary tumors are exceedingly rare. They are generally large and invasive. The prognosis is inversely related to the size of the tumor at the time of diagnosis. Hyperthyroxinemia with inappropriately elevated or normal TSH, in the presence of a pituitary tumor and an elevated α-subunit are the diagnostic hallmarks. Concomitant secretion of LH is rare. Although surgical resection is the first line of therapy, many of these tumors are large and incomplete resections are common. Radiotherapy is administered when the resection has been incomplete, but the efficacy of radiotherapy has not been well documented. Therefore adjunctive medical therapy is essential. Clinical improvement and significant tumor reduction have been obtained with somatostatin analog therapy.

133. Severe Status Asthmaticus Requiring Inhalational Anesthesia. M. Forman, MD, T. Kalb, MD. Division of Pulmonary and Critical Care Medicine, Mount Sinai Medical Center, NY.

A 49-year-old male was admitted to the Mount Sinai Medical Center Medical Intensive Care Unit with severe bronchospasm. Conventional treatments including intravenous steroids, beta-agonists, and mechanical ventilation were ineffective in this case. Inhalational anesthesia provided ventilatory support, and an airflow meter was used to measure exhaled tidal volumes as a gauge to therapy. Bronchodilation was achieved and the patient recovered.

134. Clinical Case Presentation: Jaundice in a Patient with Prostate Cancer. C. Frissora-Rodeo, A. Rosman, A. Marshall, B. Reiter, and F. Paronetto. The Mount Sinai Medical Center, Department of Medicine.

A 72-year-old man was admitted because of jaundice and pruritus. Three days prior to admission the patient noted pruritus, jaundice, and tea-colored urine. He denied fever, abdominal pain, nausea, and vomiting. He was diagnosed with adenocarcinoma of the prostate seven years prior to admission. He was treated with radical prostatectomy at that time and serial imaging studies revealed no evidence of metastatic disease. He was well until three months prior to admission when he underwent an above-the-knee amputation after a motor vehicle accident. He required transfusion of packed red blood cells postoperatively. A repeat bone scan revealed metastatic disease in the spine and the iliac crest. Abdominal CT scan revealed enlarged retroperitoneal lymph nodes and the liver appeared normal. He was treated with orchiectomy and flutamide. The medical history was significant for diabetes mellitus, hypertension, and an inferior wall myocardial infarction. He formerly was a bartender and consumed 16 ounces of whiskey per day. His last drink was thirteen years ago. Medications included flutamide, hydrochlorthiazide, NPH insulin, and salicylic acid.

On examination the patient was awake and alert. The temperature was 38 degrees, the pulse was 76, and the respirations 14. The blood pressure was 120/70. The skin was jaundiced and the sclerae icteric. The lungs were clear, and the heart sounds were normal. The abdomen was mildly obese, and there were no caput medusae or angiomas. The bowel sounds were normal and the abdomen was soft with mild right upper quadrant tenderness. There was no organomegaly, mass, or evidence of ascites. Rectal exam revealed no masses and light stool which was negative for occult blood. Laboratory studies revealed: white cell count 7,200/mm^3 with a normal differential; hemoglobin, 10 gm/dL; platelets 228,000; total bilirubin, 13 mg/dL; direct bilirubin 8 mg/dL, aspartate aminotransferase 305 U/L; alanine aminotransferase 443 U/L; alkaline phosphatase 3054 U/L; gamma-gutamyl transpeptidase, 669 U/L; and prothrombin time, 11 seconds. Hepatitis serologies were negative. Urinalysis was significant for bilirubinuria. Five weeks prior the bilirubin, ALT, and AST were normal. Abdominal sonogram and abdominal CT scan revealed no evidence of liver metastasis, bile duct dilatation, or gallstones. Liver biopsy revealed significant intrahepatic cholestasis, feathery hepatocytes containing granules of bile pigment, and focal necrosis of hepatocytes surrounded by a prominent accumulation of neutrophils and mononuclear cells. These features were interpreted as being drug induced. Flutamide was discontinued on admission. The total bilirubin decreased to 2 mg/dL one month after the flutamide was discontinued.

The patient remains well, and is living at home.

135. Clinical Case Presentation: Sudden Death in a 60-Year-Old Tennis Player. C. Frissora-Rodeo, B. Fyfe, S. Rodeo. The Mount Sinai Medical Center, Department of Medicine and Department of Pathology.

A 60-year-old man consulted an orthopedic surgeon with a complaint of right neck pain. He was in good health until ten days prior when he developed a nonproductive cough and myalgia. Two days prior, the patient played nine sets of tennis and was struck by a tennis ball on the right mastoid process. For 24 hours following this injury he complained of increasing sharp right neck pain, with occasional radiation to the right scapula and hand. The medical history was significant for occasional viral syndromes and cervical spondylosis. The surgical history included complete resection of well-differentiated papillary carcinoma of the right thyroid and intussusception in infancy. Otherwise he was in extremely good health, and engaged in competitive tennis regularly. The patient was an entrepeneur chemical engineer, and served in the Korean War. There was no history of obesity, hypertension, tobacco use, hypercholesterolemia, or diabetes. He consumed three glasses of wine approximately four times per week. Three brothers developed coronary artery disease at approximately age 55. Medications were: levothyroxine .175 mg daily and ibuprofen 400 mg p.o. every eight hours as needed.

Upon examination he was in moderate discomfort. Physical examination was significant for cervical muscle spasm. Plain X-ray revealed degenerative changes in the cervical spine. He was treated with a cervical collar, naproxyn, acetaminophen, tylenol, and cyclobenzaprine. An MRI was scheduled. The patient continued to complain of neck pain which was partially relieved by the above medications. He noted myalgia, a nonproductive cough, pharyngitis, arthralgia, anorexia, one episode of nonbloody vomiting, and occasional tachypnea when the neck pain was severe. During the MRI he was tachypneic but otherwise had no orthopnea, palpitations, or edema.

Four days after the office visit, during a telephone call to his orthopedic surgeon, the patient complained of malaise, increasing right arm and neck pain, and decreased ability to move his right arm. The surgeon noted mild confusion which he attributed to cyclobenzaprine, which was replaced with diazepam. The patient returned home, did not ingest diazepam, and fell asleep. Several hours later he had labored breathing and a cardiopulmonary arrest. EMS found the patient to be in asystole and then in ventricular fibrillation. ACLS protocol was initiated. The patient was dead on arrival to the emergency room.

Post-mortem examination revealed: white blood cell count 12,500/mm^3 with neutrophils 66%, bands 7%, lymphocytes 19%, monocytes 8%; normal thyroid function tests; and Coxsackie B1, B3, and B6 titres of 1:32. Polymerase chain reaction for Cocksackie B viral particles was negative. The heart weighed 450 g, the left ventricular wall thickness was 1.5 cm, and the valves were normal. Microscopic exam revealed focal myocarditis with infiltration of histiocytes and occasional eosinophils, predominantly in intersitial tissue planes. These findings were interpreted by two experts as a hypersensitivity reaction. The pathology was not consistent with a viral myocarditis, due to lack of lymphocytic infiltration.

136. Clinical Case Presentation: Syncope after Cocaine Use. Christine Frissora-Rodeo, MD and Alain Zilkha, BA. Department of Medicine, The Mount Sinai Medical Center, New York, NY.*

A 61-year-old man was admitted for the evaluation of shortness of breath and palpitations. He was well until two weeks prior to admission when he had a syncopal episode while dancing. He complained of palpitations prior to the event. No seizure activity was noted. He had consumed alcohol and used nasal cocaine approximately three hours prior to the syncopal episode. He subsequently developed progressive dyspnea, low grade fever, and was treated at an outside clinic with Erythromycin. He then noted orthopnea, palpitations, and paroxysmal nocturnal dyspnea. There was a history of rheumatic fever at age 18. He reported thirty sexual partners in the last three years and used cocaine biweekly. He was never tested for antibody to HIV. He was employed in a textile factory.

On physical examination the patient appeared in severe respiratory distress. The temperature was 37.6 degrees centrigrade, the pulse was 136 and irregular, and respirations were 46. The blood pressure was 130/70. The inspiratory drop in systolic blood pressure was three. Venous pulsations were visible at the level of the mandible. There were decreased breath sounds and bilateral rales at the lung bases. Diffuse wheezing was also present. The heart rate was tachycardic and irregular. A II/VI diastolic murmer was heard at the apex in the left lateral decubitus position, and a III/VI holosystolic murmur was heard at the apex which radiated to the axilla. The abdomen was soft, and there was mild edema in the extremities. Laboratory data revealed: white blood cell count, 8,700/mm^3 with a normal differential; hemoglobin, 13.3 gm/dL; platelets 288,000, potassium 4.6 meq/liter; creatinine 1.1 mg/dL; creatinine kinase 89 U/L; lactate dehydrogenase 412 U/L; and normal thyroid function tests. EKG revealed atrial fibrillation at 130 and right bundle branch block pattern. HIV antibody was negative. Echocardiogram revealed moderate mitral stenosis, mild mitral regurgitation, a markedly dilated left atrium, and a right ventricular systolic pressure of 70 mm. The right ventricle was dilated with decreased function. Cardiac catheterization after diuresis revealed a mitral valve area of 1.4 cm^2, moderate mitral regurgitation, and a transmitral gradient of 8 mm Hg. The pulmonary capillary wedge pressure was 30 mm Hg before and 50 Hg mm after dye injection. The left ventricular function and coronary arteries were normal.

The patient was treated with furosemide, atenolol, heparin and coumadin. He has returned to work and is well.

137. Maffucci's Syndrome with Portal Colopathy: Case Report. James George, M.D. Division of Gastroenterology, Mount Sinai Medical Center, NY, NY.

The patient is a 45-year-old white female with a diagnosis of Maffucci's syndrome, characterized by an abnormal growth pattern with elongation of the left side of her body, multiple bony deformities and enchondromatosis. In May 1992 the patient went to an outside hospital with an acute massive lower gastrointestinal bleed and underwent emergent subtotal colectomy with ileorectal anastomosis. The patient was told she had ulcerative colitis and was discharged. The patient came to Mount Sinai in March 1993 with bright red blood per rectum. Upper endoscopy revealed diffuse gastric varicies. Colonoscopy revealed an inflamed rectum with granularity and intense friability of the rectal mucosa, a normal ileum and external hemorroids. A duplex sonogram revealed cavernous transformation of the portal vein, with large varicies in the hilum and stomach. Angiography revealed cavernous transformation of the portal vein with dilated veins surrounding the rectum. The patient underwent a gastroepiploic to internal iliac vein potosystemic shunt for intractable bleeding and her portal venous pressure dropped from 30 mm to 15 mm of mercury. Preoperatively the patient lost 25 units of blood and postoperatively 2 units of blood.

This case represents an unusual manifestation of Maffucci's syndrome with portal colopathy, a condition that can be misdiagnosed as ulcerative colitis.

138. Fever, Night Sweats, and Weight Loss in a 55-Year-Old Man. Jonas Leibowitz, MD, Eric Grubman, MD, William Suozzi, MD.

A 55-year-old black male was admitted to the hospital complaining of several weeks of anorexia, exertional dyspnea, low grade fevers, night sweats, fatigue, and significant weight loss. The patient had been well until several weeks before admission, when he noticed anorexia without associated nausea or vomiting. He complained of three weeks of night sweats and arthralgias. He also noted a 35-lb weight loss of the previous several months. On the day of admission, the patient consulted his physician with the above complaints and described significant exertional dyspnea. The patient worked as an accountant. His wife and child were well. There was a 30-pack year history of cigarette smoking and the patient ingested alcohol until ten years earlier when he was hospitalized for alcoholic pancreatitis and required blood product transfusions. Many years earlier he was hospitalized for bacterial pneumonia, and six years ago he suffered a CVA with mild residual weakness in his left upper extremity. The patient's father died from a pulmonary embolus at the age of 38 and his mother was alive and had previously had a stroke. The patient had a positive tuberculin reaction and was treated with INH many years ago. His medications consisted of a thiazide diuretic and coumadin. The remainder of the history was unremarkable.

On physical examination, the patient was febrile to 102 degrees. The pulse was 104 and respirations were 18. The blood pressure was 120/74. The patient was thin and appeared younger than his stated age. No cutaneous lesions or lymphadenopathy was found. The head, neck, heart, and abdomen were normal. The lung exam revealed diffuse end-expiratory wheezes. The rectal, genital, extremity and peripheral pulse exam were normal. The neurological exam revealed mild left upper extremity weakness. The hematocrit was 30.6 percent; the white-cell count was 3900, with 80 percent neutrophils and 12 percent lymphocytes; the platelet count was 180,000, and the ESR was 85 mm per hour. The serum chemistries were normal. The arterial blood gas revealed a pH of 7.46, a pCO2 of 34 mm Hg and a pO2 of 84 mm Hg. Radiographs of the chest revealed no lymphadenopathy and changes consistent with chronic lung disease. A ventilation-perfusion scan was indeterminate and possibly consistent with severe lung disease. A pulmonary angiogram revealed no evidence of a pulmonary embolus. The patient was anergic.

The patient was started on an inhalational bronchodilator. A CT scan of the chest and abdomen with intravenous contrast revealed paratracheal and subcarinal lymphadenopathy, bullous changes at the bases, a small nodular density in the right lower lobe, and a small pericardial effusion. Multiple blood cultures were sent, all of which remained negative. The patient remained febrile. Iron studies were consistent with anemia of chronic disease with a markedly elevated ferritin. A test for human immunodeficiency virus (HIV) antibody was negative and lymphocyte studies revealed a normal CD4:CD8 ratio. An ANA and anti-ds DNA was positive. Additionally, anticardiolipin antibodies and a rheumatoid factor were positive and complement levels were low.

A diagnosis of SLE was made. The patient was started on tapering doses of prednisone, as well as plaquenil. His symptoms gradually resolved. The patient was discharged with a diagnosis of SLE and chronic lung disease.

139. A Case of Acute Pulmonary Renal Syndrome. Jill Ritter and Leslie Dubin Kerr. Division of Rheumatology, Mount Sinai Medical Center, New York, NY.

A 42-year-old Hispanic woman consulted a physician for renal failure and shortness of breath with a vague prolonged history of constitutional symptoms, anemia, and synovitis. She denied fever, cough, chest pain, or hemoptysis. Her physical exam on admission: VS: BP = 120/70, HR = 110, RR = 34, afeb. Lung: exam revealed bilat rales and rhonchi throughout; Cor: tachycardia without murmurs. Extremity exam showed palpable purpura on one fingertip, no edema or synovitis. Neuro exam was nonfocal. Lab data of note: WBC = 4.7, Hb = 5.1, Hct = 14.8. Na = 141, K = 3.9, Cl = 115, HCO_3 = 16, BUN/cr = 60/7.2. Urine sediment showed RBC casts. There was no evidence of hemolysis. CXR showed diffuse bilat infiltrates, and ABG on RA = 7.35/28/68. Serologies included: ANA 1:640, anti-DS-DNA neg., anti-Smith antibody neg., anti-glomerular basement membrane antibody neg., C3 low at 67, C4 normal. P-ANCA positive 1:320; C-ANCA negative.

Patient was admitted to MICU with acute pulmonary renal syndrome; the differential diagnoses include Goodpasture's syndrome, Wegener's granulomatosis, or systemic lupus. Pt. received 2u PRBC; Medrol 1gm IVSS QD × 3d, and plasmapheresis pending diagnostic workup. Renal biopsy showed crescentic necrotizing glomerulonephritis, and oral cyclophosphamide was started. Plasmapheresis was discontinued when immunofluorescence of renal bx. showed only small complement deposits, no linear deposits c/w Goodpasture's syndrome. Electron microscopy confirmed pauci immune necrotizing glomerulonephritis c/w Wegener's granulomatosis.

Patient was discharged on the eleventh hospital day on prednisone 60mg QD and cytoxan 100mg PO QD. Her creatinine decreased to 3.5, and CXR showed almost complete resolution of bilateral infiltrates.

140. A Case of Connective Tissue Disease Complicated by Vasculitis, Gangrene, and Tamponade. Jill Ritter, Leslie Dubin Kerr. Division of Rheumatology, Mt. Sinai Medical Center, New York, NY 10029.

A 20-year-old black woman had a 4-year history of undefined CTD manifested by cutaneous scleroderma, active myositis, Raynaud's phenomenon, necrotic hands and feet, blurred vision, and SOB. Admission physical exam was significant for cachexia VS: BP = 120/70 w/o pulsus; HR = 130; RR = 24, afeb. Wt = 65 lbs., ht = 5′6″. HEENT: alopecia, oral ulcers. Fundoscopic exam revealed inflammatory infiltrates with pale optic nerve on left. Cor: tachycardia with a gallop, pos. JVD. Lung: bilat. rales half way up. Ext. exam revealed black necrotic dry gangrene 18/20 digits to PIP joints, left wrist drop, and diffuse sclerodermatous skin with pressure ulcers. Lab data of note included Hct = 22%, elev. LDH, and Coombs pos.; normal creat.; U/A: moderate blood, no protein; CPK = 79; albumin = 1.9. Numerous autoantibodies were positive including: ANA, anti-DS-DNA, anti-RO, anti-Scl-70, Anti-RNP antibody, anticardiolipin antibodies of IgG and 1gM classes. C3 level was decreased at 65. CXR showed water-bottle-shaped heart and EKG revealed sinus tachycardia with low voltage. Echocardiogram confirmed pericardial tamponade, and GBPS showed EF = 20%.

The patient was treated with high dose IV steroids without improvement. She required a pericardial window for refractory pericarditis, and cytoxan was started for vasculitis. She also received IV gamma globulin and plasmapheresis. Our clinical impression was mixed connective tissue disease complicated by vasculitis of the retina, digital arteries and peripheral nerves, cardiomyopathy, tamponade, thrombosis secondary to antiphospholipid syndrome, and malnutrition. After a stormy four-month course complicated by persistent exudative drainage from pleural/pericardial drains, catheter sepsis, esophagitis, GI bleeds, she is currently markedly improved. There is no reaccumulation of pleural/pericardial effusions. Repeat GBPS shows EF = 36%, no deterioration of vision, and resolution of wrist drop. Digital gangrene has not progressed; necrotic tissue is autoamputating. Her weight is now 88 lbs., and albumin, 3.8.

141. Ischemic Ulcerations of the Rectum in a Patient with Primary Antiphospholipid Syndrome. Jill Ritter M.D. and Tony Weiss M.D. Divisions of Rheumatology and Gastroenterology.

A 53-year-old black woman had a history of end stage renal disease on hemodialysis for one year. One day after her repair of a clotted graft she developed monocular blindness of the right eye. Ophthalmalogic exam was suggestive of ischemic retinopathy. The patient had an ESR of 100 and was started on high dose steroids for presumed temporal arteritis. Transthoracic echocardiogram and carotid Dopplers were negative. CT scan of the head revealed a right occipital infarct. A temporal artery biopsy was negative and steroids were tapered. The patient was admitted with fluctuation in her mental status while on 40 mg qd of prednisone. She was febrile to 100.7 on admission but physical exam was otherwise unremarkable. Repeat CT scan revealed a possible left caudate lobe infarct. EEG and lumbar puncture were unremarkable. Cultures of blood and cerebrospinal fluid were negative. Steroid related delirium was suspected and the taper was continued. On the tenth hospital day she passed a large amount of bright red blood per rectum. She became hypotensive, requiring fluid resuscitation, transfer to intensive care, and transfusion of five units of PRBCs. An upper endoscopy revealed superficial gastric erosions. Colonoscopy was remarkable for ulcerations of the distal rectum and necrotic-appearing tissue. Biopsy showed focal superficial necrosis suggestive of ischemic mucosal injury.

Serologic studies revealed an IgG antiphospholipid antibody titre of 6.8 (nl < 3) and a negative ANCA. The angiographic studies of the mesenteric and iliac vessels were normal. The patient was treated initially with a rectal suspension of carafate and subsequently with intravenous heparin. On day 19 a repeat endoscopic exam revealed significant healing of the ulcers. She remained without evidence of recurrent bleeding and continues on long-term anticoagulation.

Gastrointestinal complications of primary antiphospholipid syndrome are rare and have previously been reported to result in intestinal ischemia and infarction. We believe that this case is important in showing that ulcerations of the rectum can be seen with this disease and may present with significant bleeding.

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4 **Soc for Clinical and Experimental Hypnosis: Introductory Clinical Hypnosis Workshop**
Marianne S. Andersen, PhD
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Manipulating the Mouse Embryo: From Cells to Genes
Janet Rossant, PhD, Mt Sinai Hosp of Toronto

DECEMBER 1993

Training in Child Abuse Recognition & Reporting
6 PM Hatch Aud
Katherine Teets Grimm, MD
repeated 2/1, 3/29, 6/28

The Dean's Lecture Series, 4 PM Hatch Aud
Using an Ancient Enzyme to Regulate the Fate of RNA: How Eukaryotes Sense and Control a Toxic Nutrient
Richard D. Klausner, MD, Natl Institutes of Health

Myofascial Pain: Diagnosis & Treatment
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Symposium on Women's Health Care Issues in the 90's: For Primary Care Providers
Michael Brodman, MD
Martin E. Goldman, MD
Stacey E. Rosen, MD

The Dean's Lectures Series, 4 PM Hatch Aud
Memory and the Mind
Patricia Goldman-Rakic, PhD
Yale University School of Medicine

Brachytherapy for Prostate Cancer
Nelson N. Stone, MD

Queens Hospital Center Internal Medicine Board Review Course
Wednesday evenings through June 1994
Laguardia Marriott Hotel
Fred Rosner, MD

American Academy of Psychiatry and the Law Conference
Karl M. Easton, MD

27 **International Trauma Anesthesia & Critical Care Soc: 1994 Trauma Anesthesia Update**
Lake Tahoe, California
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9 **The Dean's Lecture Series, 4 PM Hatch Aud**
Molecular Properties of Voltage Gated Ion Channels
William A. Catterall, PhD
Univ of Washington School of Medicine

MARCH 1994

4 **Issues in Medical Ethics 1994: Scientific Medicine, Alternative Care, and Third-Party Payers**
Rosamond Rhodes, PhD

9 **The Dean's Lecture Series, 4 PM Hatch Aud**
Mechanism & Regulation of Protein Transport Early in the Secretory Pathway
Randy Schekman, PhD
University of California at Berkeley

5–12 **Skull Base Surgery**
Chandranath Sen, MD & Peter Catalano, MD

Head & Neck Reconstruction
Mark Urken, MD
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18 **25th Annual Communications Disorders Conference**
Arnold Shapiro

APRIL 1994

7–8 **Alternate Treatments for Localized Carcinoma of the Prostate: Radical Perineal Prostatectomy, Brachytherapy, Cryosurgery**
Nelson N. Stone, MD

13 **The Dean's Lecture Series, 4 PM Hatch Aud**
New Concepts in Steroid Receptor Activation
Bert O'Malley, MD
Baylor College of Medicine

20–22 **Aortic Surgery Symposium IV**
New York Hilton & Towers
Randall B. Griepp, MD

22–23 **Thyroid Disease and the Eye**
Arthur L. Millman, MD

MAY 1994

7 **Conference on Mediastinal Diseases**
Steven M. Keller, MD
Paul A. Kirschner, MD

8 **Echocardiography Workshop**
Martin E. Goldman, MD

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Louis E. Teichholz, MD
Richard Gorlin, MD
Simon Dack, MD

11 **The Dean's Lecture Series, 4 PM Hatch Aud**
Signal Transduction by Receptors that Regulate Tyrosine Phosphorylation
Joseph Schlessinger, PhD
NYU School of Medicine

JUNE 1994

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The Salk Institute For Biological Studies

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Education, Clinical Services, and Research on Treating Older People:

The Department of Geriatrics and Adult Development, The Mount Sinai Medical Center—A Decade of Experience

Myron Miller, Rein Tideiksaar, and Carol Capello, guest editors

From the Department of Geriatrics and Adult Development,
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Education, Clinical Services, And Research On Treating Older People:
A Decade of Experience

Introduction

ROBERT N. BUTLER, M.D.
Brookdale Professor and Chairman
Department of Geriatrics and Adult Development
Mount Sinai School of Medicine
The Mount Sinai Hospital

THE GOAL of the Department of Geriatrics and Adult Development is to improve the quality of life of older people through excellence in patient care, professional and public education, biomedical and clinical research, and public policy development. The Department strives to serve as a model and catalyst for academic geriatrics in the United States.

Mount Sinai is a fitting home for this first and only Department of Geriatrics in an American medical school since this institution has a unique history of contribution to the development of geriatrics. In 1909 Ignatz L. Nascher, a Mount Sinai physician, introduced the word geriatrics, and in 1914 he authored the first American textbook of geriatrics. Alvin Goldfarb pioneered geriatric psychiatry both at Mount Sinai and the Jewish Home and Hospital for Aged (JHHA), where Frederick Zeman contributed to the development of geriatric medicine and also wrote historical articles on geriatrics.

Mount Sinai continued its role as the pioneering home of geriatrics with the establishment of the Department of Geriatrics and Adult Development 10 years ago. Thomas Chalmers, then president and dean, and Albert Stern, then chairman of the Board of Trustees, agreed to create a full-scale department that could claim curriculum time for geriatrics throughout the medical school career, including a fourth-year required rotation, that would have a relationship with a "teaching nursing home," and that would include inpatient beds and an outpatient clinic. These goals, as well as others, have been met in the department's first decade.

We worked to establish a science base in molecular biology, neurobiology, and the immunology of aging. We were able to establish the endowed Mathers chair in molecular biology and the Johnson chair in neurobiology and to place the professors in the relevant centers at Mount Sinai to insure the strength that comes from having a critical mass of collaborators as well as shared resources. The Brookdale Foundation, which supported our tenth anniversary celebratory symposium "Strategies to Delay Dysfunction in Later Life," has also supported an endowed professorship and many of the department's efforts. We look forward to having space in Mount Sinai School of Medicine's new research building, where we expect to establish a major laboratory on aging and longevity with special emphasis on neural aging. The central nervous system—the mind—is the essential pacemaker of aging, both in the biological sense and in terms of quality of life, since the central nervous system and mental faculties are essential for personal adjustment and social adaptation.

The Greenwall chair is the first endowed chair for a professorship shared between a long-term care institution, the Jewish Home and Hospital for Aged (JHHA), and a medical school. We have enjoyed an extraordinary partnership with the JHHA. With a "bridge nurse," we have created opportunities to study the nature of patient transfers from JHHA to Mount Sinai, as well as to insure the best care.

Education and Clinical Services

As a full-scale department, we have carried out undergraduate, postgraduate, and continuing medical education, provided clinical services, and conducted research. In addition, we have undertaken policy-related studies, pursued community activities, and supported studies in bioethics. We have developed special clinics devoted to the top three concerns in geriatrics: dementia, problems of mobility, and incontinence. In coordination with the Department of Obstetrics and Gynecology, we established New York City's first osteoporosis clinic, and with the Department of Psychiatry, one of the National Institute on Aging Alzheimer's Disease Research Centers.

High-quality education in any branch of medicine is impossible without the availability of fine clinical services. Mount Sinai is, therefore, fortunate to have two excellent sites at which students see the principles of geriatrics at work. One is the Geriatric Evaluation and Treatment Unit, endowed by the Eisner Family Foundation and housed in the Guggenheim Pavilion. The other is the outpatient clinic, which was endowed by Phyllis and Lee Coffey.

Medical teaching and learning depend not only on first-rate clinical services but also on exposure to the processes of scientific inquiry. In scientific inquiry, the first activity is careful observation. The second is hypothesis-building, wherein a proposition to be tested has an equal chance of being refuted or confirmed. This happens in fine medical diagnostic inquiry as well as in research. The department believes students at all levels need to be exposed to these processes of scientific inquiry, and it supports research electives by students and research by fellows.

Recruiting outstanding young people into the field of geriatrics is vital, but it is extremely difficult. Nationally there are relatively few role models in geriatrics. In general, interest in primary care medicine is declining, and physician reimbursement for primary care and geriatrics is not competitive. Training funds are minimal, and there has not been a major national initiative to support geriatrics comparable to the support of, for example, cardiology. After the National Heart Institute was established in 1947, some 16,000 cardiologists were trained during the first 22 years. Nothing like that occurred with the establishment of the National Institute on Aging, despite our wishes.

There are, however, some efforts underway to enhance education in geriatrics. The Brookdale Foundation's National Fellowship Program, which I chair, has helped create an outstanding coterie of young people and moved them beyond their fellowships into junior faculty positions in geriatrics and in social and behavioral gerontology. And the Commonwealth Fund, with the help of the Alliance for Aging Research, is now engaged in trying to develop a national physician-scientist program in geriatrics.

I presented the concept of a federal geriatrics initiative before the Senate Special Committee on Veterans' Affairs, chaired by Senator John D. Rockefeller IV, in May 1993. Funds drawn from the Medicare graduate medical education program and from Veterans Affairs would be coordinated (without damage to existent residency programs) to foster the development of academic geriatrics within each of the 126 medical schools through core funding. Incentive payments would go to those medical schools that develop additional specific programs, such as relationships with teaching nursing homes, home care programs, a healthy elderly program, a hospice program, mandated clerkships. We have made similar suggestions before the New York State Legislature.

Also in the Department's education repertoire, our Healthy Elderly program at the 92nd Street Young Men's-Young Women's Hebrew Association, with the inspired support of Janet Fisher, has helped students overcome the negative stereotypes about old age that follow from exposure only to sick and demented older persons. Hunter College's Brookdale Center on Aging, superbly directed by Rose Dobrof, and the department have co-sponsored the federally supported Geriatric Education Center, which helps educate a wide variety of health and social service providers in geriatrics.

Community and Policy Concerns

Our involvement in the East Harlem community is perhaps best illustrated by our medical home care program and by Project Linkage, which is currently in development. The purpose of Project Linkage is to create shared housing for older persons in East Harlem, incorporating an after-school enrichment program for latchkey children between 5 and 12 years of age. The enrichment program would include tutorials provided by retired older persons, which demonstrates one way of using a still-productive reservoir of great talent.

We established in 1990 the International Leadership Center on Longevity and Society (ILC) together with Japanese colleagues. The ILC is the first private, nonpartisan, nonprofit international center on research, education, and policy development devoted exclusively to the effects of longevity on society and its institutions. The ILC focuses not on individual aging, but on population aging and its impact. There are now two ILC offices, one in Tokyo and one in New York City. We hope soon to have a European center in Paris. The ILC is based on the belief that it is possible to undertake important comparative studies that will yield information of value to collaborating societies. We also believe that people who are not part of a given society may be in a good position to offer insights that are difficult for people within the society to make. So far we have been collaborating with Japan on issues of the bedridden, relationships among the generations, characteristics of the nonprofit voluntary sector, and studies of older people living alone. The endowed Harold Hatch International Lectureship in Geriatrics, part of the ILC, has brought us scholars from Europe and Japan.

The Future of Geriatrics

Geriatrics does not need to become a practice specialty. Rather, it should be primarily an academic and consultative specialty. An academic specialty provides the leaders, the innovators, and the researchers who can assure the integration and mainstreaming of knowledge about aging throughout all of primary care and specialty medicine. Geriatrics should also be involved in settings with high concentrations of older persons, such as nursing homes and retirement communities.

An unintended consequence of the diagnosis-related-groups (DRGs) methodology, which was introduced as a cost-containment strategy and has led to a shorter length of stay in hospitals, is that today it is no longer possible for a medical student to learn about the natural history of medical conditions in depth and to get to know patients and their families. To remedy this situation, I suggest that medical students follow the patient through various sites. The department's complex multisite educational program may become a model for the development of a new-style multisite (non-hospital-based) medical school of the 21st century.

As I am writing this, we all eagerly await the imminent presentation of the new health reform package by the Clinton administration. One potential problem that the administration needs to guard against in the development of the reforms is curtailing benefits that many people now have while raising taxes. A single uniform payment system is as important as a single payer methodology. In the Coffey Clinic, for an initial comprehensive evaluation of an older patient who has multiple, complex, and interacting psychosocial and physically acute and chronic problems, we receive—depending on the payer—approximately $9.50 from Medicaid, or $88 from Medicare, or an average of $122 from other third-party payers. It is not hard to see how unattractive poor and older patients are in a free market economy. But if uniform payments were made for services and procedures independent of the source of payment, such discrimination would disappear.

Discrimination by disease is also a problem. If one has a heart attack, for example, one is well covered. Yet if one has a "brain attack," such as dementia, one does not enjoy the same financial protection. The first is treated in a hospital and covered by Medicare; the second requires long-term care, for which there is Medicaid coverage only after "spending down" assets and income.

Obstacles in the development of geriatrics include not only reimbursement but the failure to have an "intensity index": the older the patient, the more complex the case and the longer both diagnosis and care take. Great Britain, for example, deals with this problem by adding to capitation payments for older patients.

Although geriatrics does not have reimbursable technological procedures, it may soon have Medicare payment codes for assessment and for coordination of care. Moreover, Medicare may soon become the template for general payments to physicians, which would put all patients on the same footing. The politics of all this is on the side of geriatrics because of economic necessity and demographic changes.

As for the future of geriatrics as it is taught and practiced in the department, we have achieved much, but there is always room for improvement. Through the JHHA, we have surveyed the 12,000 students that have been trained through our program and found that 70% appreciated having been taught geriatrics at Mount Sinai School of Medicine. The medical residents have accepted their month-long rotation through the program, but we regret that we are not able to provide them a more comprehensive education, including long-term care and other experiences, as well as continuity in their contact with patients. We hope that with time these limitations will be overcome. Of the 40 fellows who have graduated from the program, some 70% have filled academic positions in geriatrics. We are pleased that this percentage reflects the mission of the department.

We remain concerned about the central challenge of geriatrics—the maintenance and restoration of function in our older patients. We must deal with the issue more effectively in both our inpatient unit and outpatient clinic. With hospitalization comes a loss of function, and we are endeavoring to make the hospital experience less traumatic for the older patient. Another great need is to study and improve the conditions for older persons in American emergency rooms.

In this century we have increased average life expectancy at birth by 28 years in the United States. The Baby Boomers, the largest generation in U.S. history, which comprises one-third of our nation's population, will become a huge cohort of older persons between the years 2020 and 2030. In the judgment of most people in gerontology and geriatrics, our society is ill-prepared to meet the challenges that this increase will bring. Therefore, the Baby Boomer generation is very much at risk, as are the generations that will follow.

Despite advances in the field of aging, people in general continue to feel discomfort about the topic. This unease translates into denial and avoidance. The sense of immortality of adolescents is legendary; there is a comparable legendary lifelong avoidance of the intimations of aging and mortality with which we all must deal. Members of the department continue to confront the issues of ageism, as well as our societal and cultural taboos with regard to older people, including their sexuality, dying, and death.

The department's work has not been easy, and our job is not over. Because changes are imminent in both demographics and health care delivery in the United States, the future is somewhat uncertain. What is certain, however, is that geriatrics as a medical field will grow in importance and should be at the center of discussion. I hope this issue of *The Mount Sinai Journal,* "Education, Clinical Services, and Research on Treating Older People: The Department of Geriatrics and Adult Development, The Mount Sinai Medical Center—A Decade of Experience," which details the innovative programs and the accomplishments of the department, will contribute to those discussions and to their resolution.

Education, Clinical Services, and Research On Treating Older People

Education

Education in Geriatrics:

A Required Curriculum for Medical Students

Gabriel Gold, M.D.

Abstract

The mandatory geriatrics and gerontology curriculum at The Mount Sinai School of Medicine in New York includes two modules for first- and second-year students and a four-week block experience for fourth-year students. The first-year curriculum emphasizes socioeconomic, psychosocial, biomedical, and attitudinal issues. The second-year experience serves as an introduction to clinical geriatrics. The fourth-year clerkship allows students to further develop their fund of geriatric knowledge, learn specific geriatric skills, and build on their internal medicine foundation, integrating new knowledge and skills and developing into comprehensive practitioners who can apply the team approach to address all the medical, functional, psychosocial, and ethical aspects of caring for the elderly.

CURRENT CHANGES IN DEMOGRAPHICS include a dramatic increase in the elderly population in the United States, particularly in the group aged over 85 years. The proportion of individuals over age 65 rose from 4% of the total population in 1900 to 11% in 1980, and it is projected to reach 20% by year 2030 (1). The number of individuals over age 85 rose from 370,000 in 1940 to 2.3 million in 1980, and it is estimated to grow to 12.8 million in 2040 (2). Furthermore, the elderly represent a disproportionately large part of all medical consumers. Individuals over age 65 use hospitals at 2.8 times the rate of those under 65 (3) and account for 29% of all health care expenditures in the United States (4). The over-85 age group uses hospitals twice as much as those aged 65 to 69, and nursing homes 11 times as much for women and 16 times as much for men (5). It is predicted that by the year 2020, the elderly will consume nearly half of the nation's health care services (6).

The challenge of providing health care to this ever-increasing segment of the population has heightened the need to teach geriatrics in medical schools. In 1978 the Institute of Medicine recommended that appropriate content on aging be included in basic and clinical science courses and favored a required course that integrates knowledge about aging and the problems of the elderly (7). In 1983, the Association of American Medical Colleges departed from its traditional reticence in addressing categorical subjects in medical school curricula and published a guideline for geriatrics curriculum assessment, outlining ways in which courses in basic science and clinical medicine could be strengthened in the areas of geriatrics and gerontology (8). Although many medical schools now offer training in geriatrics and gerontology, the structure of these programs varies greatly in time and content; in addition, some are mandatory, others are selective, and still others are elective. Initiatives of the Department of Geriatrics and Adult Development at the Mount Sinai School of Medicine have led to both elective and mandatory undergraduate training in geriatrics.

Elective training includes research and clinical electives in geriatrics for first- and second-year students, as well as a Geriatrics Student Interest Group for those who wish to cultivate their

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interest in different aspects of the aging process. Mandatory training is described below.

Geriatrics Module in the Human Development Course

Thirteen of the total 63 hours of the Human Development course for first-year students are devoted to geriatrics. The goals of this module are to increase the student's knowledge of socioeconomic, psychosocial, and biomedical issues related to aging. Attitudinal issues are also stressed.

Lectures in the geriatric module are:

- Introduction to Geriatrics
- Aging Physiology
- Theories of Aging
- Aging Psychology
- Mental Health and Aging
- Osteoporosis
- Mobility: Gait and Balance
- Sexuality and Aging
- Sociology of Aging
- Ethical Issues

In addition to lectures, students attend a two-hour small group workshop, facilitated by geriatrics faculty, in which three to four older persons, representative of the positive aspects of aging, discuss their personal aging experiences and share their wisdom and thoughts on aging with students. The primary goal of these small groups is to help students address early in their medical careers any stereotypes they may have concerning the elderly; they see first-hand that aging can be healthy and productive. Workshops are followed by an optional reception, where interested students and elders mingle and continue their earlier discussions more informally.

Geriatrics Module in the Physical Diagnosis Course

Three hours of the second-year Physical Diagnosis course are devoted to the history-taking, physical examination, and functional assessment of the geriatric patient. Students are alerted to the major differences between obtaining histories and performing physical examinations on older versus younger people. Several points are stressed, such as the atypical presentation and multiplicity of disease and the need to examine patients for bedsores, to assess their mobility and functional and social status, and to perform a mental status examination. After a lecture, students break into small groups to observe a geriatrician taking an elderly patient's complete history.

The Geriatrics Clerkship

A required four-week geriatrics clerkship for all fourth-year students emphasizes attitudinal aspects, clinical skills, and clinical knowledge of common geriatric syndromes. The objectives of the clerkship were developed based on the medical literature (8–10) and the polling of all geriatrics faculty at a department retreat. Students rotate through one of six sites and are exposed to multiple levels of geriatric care, which may include acute geriatric care and geriatric assessment; geriatric consultation; long-term care; outpatient geriatric medicine; home care; hospice care; and well-elderly programs. The intensity of exposure to the varied aspects of geriatric medicine is dependent on the site.

The Mount Sinai Hospital is a large tertiary-care university hospital, which includes a 16-bed Geriatrics Evaluation and Treatment Unit that provides acute medical care and geriatric assessment to frail elderly persons. Students rotating through the unit are assigned two to four patients and are responsible for preparing a written history, physical, and geriatric assessment for these patients. Geriatric assessment may include functional assessment; gait and falls assessment; cognitive assessment; dental, hearing, and vision assessments; nutritional assessment; health maintenance; evaluation of skin integrity; risk of pressure sores and need for preventive measures and treatment; need for rehabilitation services; evaluation of urinary or fecal incontinence; assessment for possible elder abuse and caregiver stress; and polypharmacy assessment. Students also spend one half-day each week in the outpatient geriatric clinic, accompany a physician on home visits, and visit the Rehabilitation Department, a long-term-care facility, and a hospice.

Students assigned to the Geriatrics Consultation and Liaison Service at Mount Sinai are responsible for presentation of all new consult cases, which includes a geriatric assessment as described above. These students spend one half-day each week in an outpatient setting (outpatient clinic or private-practice office) and one day each week accompanying a hospice physician on home visits. These students also visit the Rehabilitation Department and a long-term-care facility.

Students assigned to the City Hospital Center at Elmhurst, a 780-bed municipal teaching hospital, are responsible for geriatric consultation on frail elderly patients on acute care wards. Students participate in weekly rehabilitation clinics and spend one half-day each week in the geriatric outpatient clinic and one day each week at a well-elderly program (11) that has had a positive impact on student attitudes toward the elderly (12). Students also visit a long-term-care facility.

The Jewish Home and Hospital for Aged has two campuses that serve as clerkship sites. Students at the Central House campus rotate through a 514-bed nursing facility; they are assigned both acutely and chronically ill patients and are responsible for an in-depth geriatric consultation on all medical, ethical, functional, and psychosocial aspects of each case. Students also spend at least one full day on home visits and attend rehabilitation clinic for two half-days. Students at the Kingsbridge Division campus rotate through an 816-bed nursing facility, a 300-tenant enriched housing facility, and a geriatric day-care program; they are responsible for geriatric consultation on rehabilitation patients and acutely ill nursing facility residents. Students also spend one day a week in specialty clinics for nursing facility residents, one day in an outpatient clinic, and one to two days accompanying a physician on home visits.

Students rotating at the Bronx Veterans Affairs Medical Center are assigned to a 120-bed nursing facility or to a 25-bed intermediate-care facility and a 15-bed geriatric evaluation and management unit. Students assume direct responsibility for the care of four to six residents and also spend two half-days in a geriatric home-care program.

At each of these sites, students participate in geriatric medicine rounds, geropsychiatry rounds, specialty rounds, and an ethics teaching session. Teaching methods include lectures, small group patient-management sessions, individual student oral presentations to their peers, a syllabus, a simulated patient encounter, and informal teaching during clinical activities.

Two days of core lectures are given at Mount Sinai School of Medicine during the first week of the clerkship, covering:

Introduction to Geriatrics
Osteoporosis
Cognitive Impairment
Falls and Immobility
Medical Insurance and Support Programs For the Elderly
Demographics
Health Care Costs
How Doctors Get Paid
Urinary Incontinence

Subsequent lectures on the following topics are given at each site; the topics may vary depending on clerkship site and rotation:

Rehabilitation in the Elderly
Nutrition
Restraints in the Nursing Home
Fecal Incontinence
Geriatric Dentistry and Oral Pathology
Infections in the Nursing Home
Tuberculosis
Thyroid Disease
Constipation
Sexual Dysfunction
Health Maintenance

The syllabus supports the core lecture series and is also designed for self-study. Each chapter is preceded by a list of specific learning objectives and followed by a series of test questions, clarifying for students what they are expected to learn and allowing them to test their knowledge once they have read the material.

Patient-management sessions consist of small-group precepted workshops using a paper case that often emphasizes specific aspects of geriatric medicine, stresses diagnostic reasoning and therapeutic decision making, and provides an opportunity for students to integrate and apply their newly acquired skills and fund of knowledge to real-life cases (**box**).

Ethics teaching includes informal bedside discussions, ethics rounds, and a half-day session with a faculty preceptor at which medical students are brought together, watch a videotape presentation of an ethical dilemma, discuss their opinions about the case, and relate them to basic

Patient Management Session Topics

Falls
Urinary incontinence
Fecal incontinence
Dementia
Depression
Elder abuse
Ethics
Thyroid disease
Diabetes mellitus
Malnutrition
Peripheral vascular disease
Acute abdomen
Acute cholecystitis
Peptic ulcer disease
Atrial fibrillation
Sick sinus syndrome
Syncope
Osteoarthritis
The older driver
Hip fracture
Delirium
Acute parotitis
Anemia
Polypharmacy
Nonsteroidal anti-inflammatory drugs
Digoxin toxicity
Asymptomatic carotid bruit
Hypertension
Pressure sores
Health maintenance
Stroke
Immunity and infections
Water and electrolyte disturbances
Atypical presentation of disease

ethical principles. This session is generally well received by students, who view it as a significant improvement over the lecture format previously used.

In the 1991–92 academic year, an innovative teaching method was implemented, using "standardized patients" (SPs)—individuals trained to portray real patients in a reproducible and standardized fashion. Approximately half of all fourth-year students participate in this new program, in which they take a focused history from or a physical examination of an SP in an examining room equipped with TV cameras and microphones, and answer a postencounter questionnaire addressing planned diagnostic studies and differential diagnosis. After the encounter, each SP completes a checklist of history and physical items performed, and a faculty preceptor, who watched the interaction on a TV monitor, provides feedback to students and hands them a tape of their encounter for review. The vast majority of participating students rated this new program positively.

Student grades (pass, fail, honors) are based on clinical performance and oral presentation. In addition, students must pass a final multiple choice, minimum competency, written examination.

The geriatrics clerkship has been shown to result in significant knowledge gain and has been positively evaluated by the vast majority of students (13).

Four off-campus sites are also available for a limited number of students, at the Instituts Universitaires de Gériatrie de Genève and the World Health Organization in Geneva, Switzerland, the National Institute of Aging's Gerontology Research Center and Johns Hopkins' Francis Scott Key Hospital in Baltimore, the Hôpital Broca's geriatric facility in Paris, France (University of Paris), and the Soroka Medical Center's geriatric facility in Beer Sheva, Israel (Ben Gurion University).

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The Department of Geriatrics and Adult Development offers a great variety of clinical and research-oriented experiences for students through its electives that supplement the required geriatrics curriculum. Mathew Maurer, M.D., was one Mount Sinai medical student who took advantage of these opportunities.—Myron Miller, M.D.

A Mount Sinai Student Reflects on His Experience in Geriatrics Research

MATHEW MAURER, M.D.

MY FASCINATION with the elderly began as a child and has been further cultivated throughout my medical education by formal coursework, research opportunities, and clinical experiences. All this has led to my decisions on my future career direction.

Both of my grandparents always took an active role in their nine grandchildren's lives—celebrating each birthday, each graduation, each bar or bat mitzvah, and each wedding. It was my relationship with my grandfather, Harry, however, which had the strongest impact on my life.

Harry continuously worked hard to prove his vigor. On my seventh birthday, when my parents presented me with a bicycle, Harry insisted on taking it out for a test drive—even though he walked with a cane. I will never forget how he rode, his body swaying to and fro like a pendulum, maintaining his balance only by constantly turning the front wheel right and then left. I was sure he would fall. Luckily, he didn't.

When my grandmother died, Harry was devastated and became extremely isolated. Like most men, he'd just assumed that she would outlive him. My grandmother had been the one who had done all the social planning, the one Harry had always relied on to draw him out of his shell. I'm not sure if he really liked himself after her death. He sat in front of the television all day, kept a poor diet, and rarely bathed.

The entire situation surrounding my grandfather frustrated me, and I would not permit myself to communicate effectively with him in fear of what I might learn. To me, it seemed as if Harry wanted to die, which I considered absurd and irrational. I had been so personally invested in his life that I could not let myself pursue the matter—I was afraid he would actually admit he wanted to die.

After a while my parents sought medical attention for Harry. Unlike anyone in my family, the physician was in a position to ask the questions that needed asking. More important, Harry was able to confess to him what he could not admit to his own family—that he wanted to die—and the physician, naturally more objective than Harry's family would be, was not shocked or hurt by this confession. Harry admitted that since he had spent his entire life with his wife, he felt his days now had no order and his life no direction.

It was through this interaction of grandfather and physician that I began to realize the remarkable position a physician is in both socially and psychologically. He can pose questions that need asking—questions that neither family members nor close friends can or will ask—without making the patient feel as if his privacy is being invaded, because the impetus behind the questioning is benevolent, motivated by a desire to assist, to improve, and, if necessary, to rescue. The patient can answer honestly because any psychological ramifications of his or her answers are minimized, knowing that this professional is objective, has heard similar views before, and is trained to address them.

Harry's admission of his feelings was therapeutic, because after his talk with his physician, he began to improve. He would get up early each morning, take a walk to buy the paper, and read in our backyard. Once I woke up, he would join me for breakfast and see me off to school. He never failed to let me know how proud he was of

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my accomplishments. He was happy to share once again in another's life. We once again had a great relationship, and I will always fondly remember him.

During my second year of medical school, my interest in geriatrics and gerontology was again sparked when I was introduced to the psychological aspects of illness in a Behavioral Science course. Here, I learned more about my own experiences with Harry. I came to appreciate that physical illness occurs in a social and psychological context that is unique to each patient, a context whose influences, at times, play a more important role than the biological problem itself. Reading extensively about the impact of social isolation on the health and well-being of elderly patients, I soon recognized what a close correlation there is between morbidity and mortality and social isolation.

During the summer of my third year in medical school, I was able to explore the impact of social isolation in the elderly when I received a competitive research grant issued by the John A. Hartford Foundation, which encourages future physicians to explore their interest in gerontology. Since the cornerstone of geriatric medicine is assessment and no tools to evaluate social isolation had yet been validated, I developed a short, self-administered questionnaire that could be used in a primary care geriatric setting to identify patients in whom social isolation is an associated factor in the development and perpetuation of their illness.

Though excited that I could pursue a research initiative, I was also frightened. Previously, I had considered research to be a pursuit that narrowed one's perspective and, although I supported research activities, I felt that successful researchers were so focused on their particular area of interest that they did not see the big picture. I also viewed researchers as loners who did not want to interact with others—totally in contrast to the type of physician I wished to be: well-rounded, compassionate, and intimately involved with my patients.

However, by using my personal interest and convictions to develop a hypothesis and explore it scientifically, I realized that my view of a successful investigator was incorrect; in truth, research was a natural extension of the person I wanted to be. In its inception, a hypothetical evaluation using the scientific method is narrow, focused, and somewhat constraining—similar to how sand in an hourglass meets at the center. But truly great researchers do not stop there. After proving or disproving their hypotheses, they begin to evaluate how their conclusions relate to other fields in medicine, psychology, and sociology. Now that sand in the hourglass begins to fall through its narrow focal point, mingling with all the other sand particles, all the previous proven or disproved hypotheses. The "inadequate" researcher is stuck in that narrow focal point, but the successful researcher moves on, broad-mindedly coupling his or her field of interest with that of others.

By the middle of my third year of medical school, my initial research was completed, showing

- A poor clinical consensus among health care providers for evaluating a patient for social isolation
- More frequent agreement among social workers and nurses than any other combination of health care team members
- Seven factors that are good predictors of social isolation
  - —marital status
  - —pets
  - —frequency of familial or companion contact
  - —personal evaluation of adequacy of familial or companion contact
  - —amount of television watched
  - —belief that he or she had no one with whom to discuss problems
  - —belief that if he or she died, they would not be missed by someone in their neighborhood

With the John A. Hartford Foundation providing financial support, I was able to travel to Chicago to present my research findings at the annual meeting of the American Geriatrics Society/American Federation for Aging Research.

Yet, while my commitment to care for the elderly was still strong, my research endeavor left me somewhat unfulfilled. First, the research design did not provide statistically significant results, nor was it ideal for the objective I had in mind. Second, the research was in gerontology and not geriatrics. In light of my medically based training, I believed that I could do more justice by pursuing a biologically based hypothesis.

I was able to do so during my final year of medical school. I fulfilled my fourth-year geriatrics rotation requirement in Baltimore, Md, by volunteering for a liaison program between Mount Sinai Medical Center and the National Institute on Aging (NIA). I had already decided to pursue a career in internal medicine and felt that additional experience in one of the medical subspecialties would be beneficial. On joint recommendations from the geriatrics faculty at Mount

Sinai and the administrative staff of the NIA's Baltimore Longitudinal Study, I contacted Dr. Jerome Fleg, a staff cardiologist at the Gerontology Research Center of the NIA. Once I had read numerous articles written by Dr. Fleg and his coworkers, he and I agreed on a research area absent from the current literature, an area the NIA had explored but never completed.

Through extensive data analyses, using the database of the Baltimore Longitudinal Study of Aging, a major NIA intramural research initiative, I evaluated the prevalence and prognostic significance of supraventricular tachycardia (SVT) during exercise treadmill testing in a proposed healthy population. After completing this epidemiological survey in 1,443 participants, I discovered the following:

- The prevalence of SVT during maximal exercise treadmill testing significantly increases with age in both men and women
- Exercise-induced SVT is not associated with major coronary risk factors or exercise-induced myocardial ischemia
- Episodes of SVT during maximal treadmill testing usually are limited to short asymptomatic runs and predominantly occur in older subjects
- Although the presence of exercise-induced SVT does not portend a long-term increase in either cardiovascular morbidity or mortality, individuals do demonstrate a somewhat higher rate pressure product at maximal effort than control subjects, suggesting that left atrial pressure may also be higher
- Most important, exercise-induced SVT, previously thought to have no prognostic significance, may be a marker for future SVT on rest electrocardiograms.

I presented these findings in Dallas at the American College of Cardiology's annual meeting.

I truly believe that geriatrics offers exciting research opportunities. As people are living longer, medicine is discovering that it needs to extend its database to elucidate the normal physiology for octogenarians and octogenarians-plus. Scientists are just now beginning to define what constitutes normal aging so we can differentiate pathology from senescence. For example, additional research conducted at the NIA and at Johns Hopkins indicates that an aging heart free from cardiovascular disease maintains normal cardiac output at lower heart rates by increasing the end diastolic volume. (The aging heart relies more on the Frank Starling mechanism than adrenergic response to maintain cardiac output.) The clinical correlates to this are the elderly patients with myocardial infarction who have dyspnea, as opposed to the chest pain that occurs in their younger counterparts. Thus, we do have a clear example of how normal aging physiology contributes to the altered presentation of disease in elderly patients.

Through my own research activities, I hope to contribute to the body of medical knowledge on aging and, in turn, utilize this information to formulate an understanding of age differences in disease. In this way, I hope to better enable my patients to achieve successful longevity. Looking into the future, I see myself in academic medicine, actively involved in geriatrics through various clinical, teaching, and research activities.

My experiences in geriatrics have been extremely fulfilling, both intellectually and socially. I wholeheartedly encourage others to explore this vast option available in the new medical frontier of geriatric medicine.

Geriatrics Fellowship Training at Mount Sinai Medical Center:

A Decade of Experience

MONTE H. PETERSON, M.D.

THE TENTH ANNIVERSARY of the Department of Geriatrics and Adult Development at Mount Sinai Medical Center provides an opportunity to review chronologically the history of its fellowship program in the context of the national evolution of geriatric medicine and graduate training programs. This article updates an earlier report (1) and provides some data on the outcome of the trainees who have graduated from the program.

Physician Personnel Needs in Geriatrics

An important stimulus behind the development of fellowship programs in geriatric medicine across the country has been the need for geriatrics personnel. A number of studies and reports have addressed this issue (2–7), and **Table 1** summarizes some of their results. The recommendations of the various studies are dependent on the validity of the underlying assumptions and methodologies involved. The most recent estimates come from Reuben and colleagues (6, 7).

The first of the most recent studies (6) deals with the need for physicians (nonsurgical physicians and geriatricians) to provide medical care to the elderly. Three different economic scenarios were considered: moderate growth, recession economy, and steady growth. The projected need for internist and family-physician geriatricians for the year 2000 ranged from 3,668 (recession economy) to 9,705 (steady growth). This was predicated on an estimation of 43% of a geriatrician's time being involved in clinical care of older persons.

The other recent study (7) addresses the need for geriatrics faculty. Five specialties (internal medicine, family practice, neurology, psychiatry, and physical medicine) were considered, and within each specialty, estimates were made for both physician and nonphysician faculty. Two methods were employed, the first relying on an advisory panel's estimates of the minimum faculty needed to sustain a division, and the second method utilizing the judgment of members of the American Geriatrics Society Education Committee on the number of faculty necessary to provide a minimum core of geriatrics training for medical students and residents in the five specialties. For comparison, Table 1 gives the projected number of physician faculty in internal medicine and family practice needed to provide core training.

Fellowship Programs In Geriatrics

The nation's first geriatrics fellowship program was established in 1972 (8). As one indication of the growth of the field in the 21 years since then, the upcoming sixth edition of the *Directory of Fellowship Programs in Geriatric Medicine,* published by the American Geriatrics Society, will list approximately 150 programs (9). However, this is likely to be an inflated number, since a review of the fifth edition (10) shows that this number includes both fellowship and residency training programs (that is, geriatrics training within internal medicine and family medicine residency programs). In addition, the listing includes anticipated as well as actual programs and

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TABLE 1
Estimates of Personnel Needs in Geriatrics

Year	Study (ref. no.)	Estimated need	Time frame
1980	RAND/UCLA (2)	7000–10,000 geriatricians (academic and practicing)	1990
1981	RAND/UCLA (3)	900–1600 geriatric medicine faculty	2000
1987	Institute of Medicine Committee on Leadership for Academic Geriatric Medicine (4)	2100 faculty geriatricians	2000
1987	Department of Health and Human Services (5)	1000–2000 academic geriatricians	2000
1993	RAND/UCLA (6)	3,668–9,705 internist and family physician geriatricians to provide medical care, depending on the economic scenario	2000
1993	RAND/UCLA (7)	Physician faculty needed to provide core geriatrics training: internal medicine, 2320; family practice, 1874	Current

programs in Canada as well as the United States. The degree to which fellowship programs are, in fact, meeting the need for geriatrics personnel (especially the need for academic geriatricians) was addressed by Reuben et al., who estimated that, due to attrition, only "25 percent of those who are [fellowship] trained to be geriatrics faculty will actually achieve senior faculty status" (7). They further point out that even if fellowship positions increased in number by 50%, attrition would result in a net loss of geriatrics faculty. The optimal way to meet personnel needs in geriatrics is currently a topic of much debate within the field (11, 12).

Mount Sinai Fellowship Program—Initial Formulation

Eight fellows began their training in geriatrics at The Mount Sinai Medical Center (MSMC) in July 1983. It is helpful to conceptualize the clinical training of the geriatrics fellowship program as having block and longitudinal components (**Table 2**). In addition to Mount Sinai, the initial clinical training sites were Mount Sinai's teaching nursing home, The Jewish Home and Hospital for Aged (JHHA), and the Elmhurst Hospital Center.

Block Components

Geriatrics Inpatient Unit. Two fellows were based in the department's fledgling Geriatrics Inpatient Unit, where they provided primary care to the patients, as well as geriatric assessment and management.

Geriatrics Consultation Service. Through its activities, the Geriatrics Consultation Service soon established itself as the department's most wide-ranging contact with the rest of the hospital. In addition to responding to requests for consultation, fellows evaluated patients in the emergency room for possible admission and followed up patients known to the department who were hospitalized on units other than the Geriatrics Unit (for instance, a Geriatrics Clinic patient hospitalized on the surgical service).

Geropsychiatry. The fellow on the geropsychiatry rotation assumed primary care responsibility for a cohort of four to five patients on the inpatient Geropsychiatry Unit. The focus of the

TABLE 2
Mount Sinai Medical Center Geriatrics Fellowships Block and Longitudinal Components, 1983 and 1993

	Block rotation	Longitudinal component
1983		
Year 1	Geriatrics Inpatient Unit	Geriatrics Clinic
unspecified	Consultation Service Geropsychiatry Skilled Nursing Unit/ Rehabilitation Unit, JHHA City Hospital Center at Elmhurst	
Year 2	Research	
1993		
Year 1	Consultation and Liaison Service Group Practice, JHHA Rehabilitation, JHHA Bronx VAMC Research I	Coffey Geriatrics Clinic Longitudinal model, JHHA
Year 2	Geriatrics Evaluation and Treatment Unit Geropsychiatry Special Emphasis Research II	

At Mount Sinai Medical Center unless otherwise specified: JHHA, The Jewish Home and Hospital for Aged; VAMC, Veterans Affairs Medical Center.

rotation was geriatric psychopharmacology and the "medical-psychiatric interface," such as the management of a depressed patient with cardiac conduction disease.

Skilled Nursing and Rehabilitation Units, JHHA. Most fellows received their first introduction to nursing homes and nursing home care at The Jewish Home and Hospital for Aged. Three of the skilled nursing units at the Manhattan Division of JHHA were designated teaching units. A rehabilitation unit was created, utilizing approximately half of the beds on one of the units. During the first year of the fellowship, each fellow on this rotation had primary care responsibility for residents at both levels of care (skilled nursing and rehabilitation).

Elmhurst Hospital Center, Queens. At Elmhurst, the site of the first geriatrics fellowship program in the United States, the activities of the fellow centered on the 72-bed skilled nursing unit existing within the hospital. The fellow on this rotation worked closely with geriatrics nurse practitioners, both on the Skilled Nursing Unit and in the Geriatrics Clinic.

Research. From its outset, the fellowship program was designed with six months of protected time for research during the second year.

Longitudinal Component

Coffey Geriatrics Clinic. Ongoing clinical experience and training was provided in the Phyllis and Lee Coffey Geriatrics Clinic, where fellows worked one or two half-days per week as part of an interdisciplinary team.

Developments Since 1984

Major changes in the fellowship program have since evolved.

1984–1985. During the academic year 1984–85, two didactic research seminar series were initiated. The objective of "Human Aging Research" was to give fellows an appreciation of both the generic issues in aging research (such as funding) and the specific topics currently being pursued by department faculty. This was followed by a course in research methods that focused on epidemiology, research design, and biostatistics. Increased time was also allotted to research by creating a protected research rotation during the first year at JHHA.

1986–1987. In the academic year 1986–87, notable changes occurred in rotations involving Mount Sinai affiliates.

At The Jewish Home and Hospital for Aged, a second longitudinal clinical component was added to the program by implementing the "longitudinal model," in which each fellow was assigned patient-care responsibility for a small cohort of residents on one of two skilled nursing floors. The program was initiated to complement the block rotations at JHHA by giving fellows continuity experience in providing long-term care over the course of their fellowship.

Out of the need to provide acute and intercurrent care to the residents on the longitudinal model came the concept of the group-practice fellow. The rotation is analogous to a private group practice, in which physicians jointly care for a cohort of patients. The group-practice fellow works closely with a geriatrics nurse practitioner and attending geriatrician and, in the process, learns nursing-home medicine as practiced in an academic nursing home.

Creation of the group-practice rotation allowed another clinical rotation at JHHA to be dedicated to the rehabilitation unit. This rotation thus evolved into the most intensive training in rehabilitation medicine during the fellowship.

During the 1986–1987 academic year, the rotation at the Elmhurst Hospital Center, Queens, was replaced by a rotation based at the Bronx Veterans Affairs Medical Center, with support from the Eastern Paralyzed Veterans Association. From its outset, the Bronx VAMC has provided training and experience in several different programs and levels of care, including the Nursing Home Care Unit, the Hospital-Based Home Care Program, and the unique opportunity to gain experience with aging spinal-cord-injury patients by fellows acting as consultants to the Spinal Cord Injury Unit.

1988–1989. National developments in geriatrics influenced continued changes in the fellowship program.

The first national Certifying Examination for Added Qualifications in Geriatric Medicine was given in April 1988. Also in 1988, the first round of geriatrics fellowship programs were accredited by the Residency Review Committees for Internal Medicine and Family Practice of the Accreditation Council for Graduate Medical Education. The Special Requirements for Residency (Fellowship) Training in Geriatric Medicine, delineated in the AMA Graduate Medical Education Directory (13) and based on guidelines for fellowship training programs developed by an Ad Hoc Committee of the American Geriatrics Society (14), helped formalize the components of the training program.

Within the fellowship program, a new rotation focused on intensive experience in the evaluation and management of syndromes common among elderly persons. This rotation utilized the department's special emphasis clinics and programs: Osteoporosis and Metabolic Bone Disease, Falls and Immobility, and Urinary Incontinence.

Another major development in the fellowship program was the institution of an optional third-year research fellowship, with support from the John A. Hartford Foundation.

1990–1991. The 1990–91 academic year marked major changes in the role of the fellow on the two major clinical rotations of the second year.

Geriatrics Evaluation and Treatment Unit. In response to a mandate from the American Board of Internal Medicine to incorporate geriatrics training in internal medicine residencies, a housestaff team from the Department of Medicine began rotating on the department's inpatient unit in July 1990. The fellow on the Geriatrics Evaluation and Treatment Unit was then able to assume a junior-attending role as leader of the team, with an emphasis on performing and teaching inpatient assessment of elderly patients.

Geropsychiatry. Implementation of the recent regulations in New York State restricting housestaff hours required an expansion in the size of Mount Sinai's psychiatry residency program. This allowed the role of the geriatrics fellow to change to that of an on-site geriatric medicine consultant, with an emphasis on assessment and management of common geriatric syndromes.

Current Status

It can be argued that (at least for geriatricians) the classic academic medicine triad of patient care, research, and education should be expanded to a tetrad by adding the realm of administration. This tetrad serves as an outline for reviewing the current status of the fellowship program.

Clinical Training

Longitudinal Components. As elaborated above, the Coffey Geriatrics Clinic at Mount Sinai and the longitudinal model at JHHA afford the fellow experience in providing continuity of care to two different cohorts of older persons.

Block Components. In the standard rotation schedule (Table 2), the duration for each rotation is ten to eleven weeks, with the exception of Special Emphasis (4–6 weeks) and Clinical Research II (26 weeks).

At the Bronx VAMC, a 16-bed geriatrics evaluation and management unit has been created, giving fellows experience in assessment of the elderly during the first year. A recent addition to the Special Emphasis rotation has been the home medical care program, in which fellows acquire experience in the delivery of comprehensive interdisciplinary care to the frail homebound elderly.

Research

Development of skills in research has been an objective of the program from its inception. To accomplish this, fully one-third of the two-year fellowship is protected research time: a two-and-a-half-month block rotation in the first year and six months during the second year.

From August through January, all fellows attend the Human Aging Research series and the research methods course, in sequence. During the first year, the Fellowship Research Committee meets with fellows individually to explore research interests and to offer assistance to those needing help in defining projects suitable for implementation. A faculty mentor is also identified at this time, and fellows are asked to submit a proposal for their research project. After a review of the literature, the fellow develops a research proposal and, if it is approved, begins data collection.

Six months of protected research time during the second year provides the fellow with time to complete the project started during the first year and in some circumstances to commence work on another project. Fellows have several opportunities to present the results of their research projects (to faculty and colleagues at a department research seminar; to a larger audience at a Fellows Research Day held in conjunction with their graduation). At the regional level, fellows participate in the annual Fellows Research Night, cosponsored by the Metropolitan Area Geriatrics Society and the Section on Geriatric Medicine of the New York Academy of Medicine. Many research projects have been accepted for presentation at the annual meetings of the American Geriatrics Society and The Gerontological Society of America.

Education

Fellows gain experience as teachers through teaching medical students and geriatrics nurse practitioner students during their clinical rotations. In addition, second-year fellows help facilitate workshops for first-year medical students during the geriatrics component of their Human Development course.

Fellows gain experience in speaking to outside professional and lay groups through participation in the department's Speaker's Bureau. Audiovisual resources are maintained for fellows' use, and they are assisted in learning techniques for creating new materials.

Administration

Fellows' interest in the administrative aspects of health care delivery, including medical practice and long-term-care administration, continues to increase. During the past several years, health policy seminars have been conducted on a variety of topics. A seminar series addressing administrative aspects of geriatric care is currently being developed.

Outcome of the Program

The "outcome" of any training program is its graduates. No data comparable to those reported by Siu et al. (15) are available at this time for graduates of our program. However, a total of 53 individuals have undertaken fellowship training over the last decade, and 43 have graduated from the two-year program. Approximately 60% of the graduates have remained within the New York metropolitan area, and 72% hold academic appointments in a large number of teaching institutions, both locally and across the country. Approximately 25% have entered full-time private practice.

Current and Future Challenges

A debate about the duration and content of geriatrics fellowship training has recently been stimulated by a proposal of Dr. William Hazzard to offer clinical one-year fellowships as an option; the reader is referred to the original article (11) and resulting letters (12).

The biggest challenge continues to be the recruitment of high-quality fellows. Comparing notes with other program directors from across the country reveals that this problem is not unique to our department. Several trends contribute to this phenomenon. First, the applicant pool is smaller, as fewer medical students are choosing the two specialties, internal medicine and family medicine, from which our applicants are drawn. In addition, residents in internal medicine are more inclined toward subspecialties that are procedure-oriented and remunerative. Also, as new geriatrics fellowship programs have been established, the competition for the available applicants has increased.

It is paradoxical that this recruitment situation prevails, given the abundant professional opportunities available to formally trained geriatricians. It is hoped that a national shift in emphasis toward primary care will result in an improved outlook for geriatrics fellowship programs and the field of geriatric medicine. We at Mount Sinai feel that our experience over the past ten years clearly demonstrates that well-trained graduates of a geriatrics fellowship program can be successful in obtaining entry-level positions in major academic centers. Through continued tracking of our graduates, we will be able to determine how well they succeed in the highly competitive world of academic medicine and how well they have met our departmental objective of training the next generation of leaders in geriatric medicine.

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Education, Clinical Services, and Research On Treating Older People

Clinical Services

The Geriatric Evaluation and Treatment Unit:

A Model Site for Acute Care of the Frail Elderly, Education, and Research

HOWARD FILLIT, M.D., AND MYRON MILLER, M.D.

GERIATRIC INPATIENT UNITS are not unique to The Mount Sinai Hospital; rather, they have been an integral component of geriatric care for over 50 years (1). Throughout the United States, a growing number of geographically based hospital inpatient geriatric units are emphasizing different aspects of geriatric care, including acute care, geriatric assessment, geriatric rehabilitation, and geriatric psychiatry (2). The Mount Sinai Medical Center Geriatric Evaluation and Treatment Unit (GETU) is an acute care geriatric inpatient unit that represents a structured approach to the complex, interdisciplinary problems of hospitalized frail elderly patients whose health care needs often extend beyond the treatment of a single acute medical illness. Since many of the unit patients have multiple chronic illnesses, the goal of geriatric care is often the restoration and maintenance of function essential to the preservation of a reasonable quality of life. The GETU also serves as a model site to foster the development of innovative and enhanced methods of care for the hospitalized frail elderly through clinical research, and it is a major teaching site for clinical geriatrics at The Mount Sinai Medical Center.

The purpose of the unit as a clinical service is best exemplified by considering two 90-year-old women. One is essentially healthy, living with her spouse at home. During the flu season, she becomes superinfected with pneumonia and is admitted to a traditional hospital bed, is given the standard 14 days of antibiotic therapy, and goes home. She does well on a traditional medical ward.

The other 90-year-old woman lives in a fourth-floor apartment in a building without elevators. She has become deconditioned, has fallen in her apartment several times, and has developed a fear of falling. She has mild cognitive impairment of unknown etiology. She rarely ventures outside and has not been to the doctor in six months, despite her long history of multiple chronic illnesses. When this patient becomes ill with the flu and pneumonia, she also develops delirium.

On her admission to a hospital, several additional health care problems are noted that may affect her outcome, including hypertension, diabetes, congestive heart failure, malnutrition, dehydration, urinary incontinence of recent onset, and a stage I pressure sore. As a result of the agitation secondary to delirium and the history of falls, she has orders for physical restraints. The patient, already incontinent of urine, now develops functional fecal incontinence. In the face of the restraints, she becomes more agitated, climbs out of bed, and fractures her hip. The stage I pressure sore soon becomes a stage IV pressure sore, complicated by osteomyelitis, requiring six weeks of intravenous antibiotics. Her malnutrition contributes to impaired wound healing and causes a secondary immunodeficiency, which predisposes her to sepsis secondary to her osteomyelitis. A vitamin B-12 deficiency goes undiagnosed, yet

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may contribute to her progressive cognitive impairment. Even if she does recover from her acute illness, she may be sent home without maximal comprehensive nursing, medical, and social services, only to return to the emergency room in a few weeks with more severe malnutrition and a worsening pressure sore or a fall. Her hospital length of stay is prolonged by the complications she suffers as well as the complex discharge planning that she needs.

The traditional medical ward may not have the expertise or resources to provide comprehensive and efficient care for such frail elderly patients with multiple complex interdisciplinary needs. The GETU is organized to bring interdisciplinary experts and resources together in a geographically based setting to provide this type of care to these patients. Indeed, several studies have demonstrated the benefits of geriatric evaluation and management programs for patient outcomes and health care costs (3).

Criteria for Admission to The Unit

The unit admits frail elderly people, generally over age 75, with complex interdisciplinary health care problems who have the potential to benefit from its unique resources (Table 1). Admission criteria have been modified from previously published criteria for admission to geriatric assessment programs operating in the Veterans Affairs but not under Medicare Prospective Payment (4). The admission criteria to the unit stress its role as an acute care geriatric unit functioning under guidelines for Medicare acute care. Several DRGs, generally underutilized by the traditional internist, may be employed, such as malnutrition, urinary incontinence, decubiti, change in mental status.

The exclusion criteria for the unit further define its function. Although the unit provides excellent palliative care to a minority of patients, it is not a hospice or terminal care unit. Nor is the unit a "geriatric intensive care unit": patients needing intensive care, regardless of age, should go to the intensive care unit. Finally, the unit is not an alternate-level-of-care unit for patients who need only social services and do not have complex multidisciplinary needs.

Unit Operation and Staff

The unit is modeled as a hospital specialty unit, much like the cardiac care unit or the stroke unit. The demographics of unit patients (Table 2) encompass the frail elderly who have complex medical and nursing problems and functional and psychosocial impairment. Although a majority of patients are currently admitted via the Emer-

TABLE 1

Admission Criteria, Geriatric Evaluation and Treatment Unit, Mount Sinai Medical Center

Inclusion criteria: Frail elderly patients requiring intensive, interdisciplinary comprehensive geriatric assessment, acute geriatric care, or geriatric specialty care

- Over the age of 65 years; generally over 75 years old
- meets Medicare Prospective Payment "guidelines" for acute care; DRGs encompassing "geriatric medicine" diagnoses, such as "change in mental status" or "malnutrition," should be considered, particularly for admissions for geriatric assessment
- has complex, multidisciplinary health care problems: multiple medical co-morbidities, nursing and social problems requiring inpatient comprehensive geriatric assessment
- has specialty problems in geriatric medicine, for example:
  - cognitive or affective disorders
  - falls, immobility, or gait disorders
  - urinary or fecal incontinence
  - malnutrition or feeding disorders
  - complications of polypharmacy
  - pressure sores
  - sensory impairments
  - sleep disorders
  - elder abuse associated with medical co-morbidities
- has potential to benefit from intensive, inpatient geriatric assessment, rehabilitation, management, or treatment services to restore function

Exclusion criteria:

- requires hospice or terminal care (patients with severe cognitive impairment occasionally admitted for acute geriatric care)
- requires intensive care; should be transferred to the intensive care unit
- requires only social services (such as nursing home placement)

TABLE 2

Summary Demographics: 233 Frail Elderly Patients, Geriatric Evaluation and Treatment Unit (4/87–7/88)

Characteristic	Data
Age	80 years
Sex	70% female
Education	8.4 years
Married	25%
Race	45% white 24% black 31% hispanic
Primary insurance	94% Medicare
No. of complicating medical diagnoses	4
Percent with psychiatric co-morbidity	56%
No. of procedures during hospitalization	3
Nursing Intensity (MEDICUS scoring)	2.3

Adapted from (7).

gency Room or the Geriatric Clinic, an increasing number are admitted specifically for geriatric assessment and acute geriatric care from the Department of Geriatrics private practice, as well as from the Department of Medicine medical wards, Internal Medicine Associates practice, and private practitioners. These referrals are greatly encouraged, since the unit is a service for the benefit of all frail elderly medical patients at The Mount Sinai Hospital. Although the unit team necessarily functions in the traditional "service" model, the unit attending physician being the attending physician during the patient's stay, the input of each patient's primary care physician is actively sought and appreciated, and patients discharged from the unit are always returned to their primary care physician with a report from the unit to insure continuity of care after discharge. Only about 10% of unit cases come from, or are discharged to, nursing homes.

Although the unit is not a high-technology unit, it does provide intensive, interdisciplinary acute care to medically complex patients. Medical care is supervised by attending physicians who are board certified in internal medicine with added qualifications in geriatric medicine, and by geriatrics fellows from the Department of Geriatrics and Adult Development. In addition to addressing the traditional medical problems that result in the acute hospital admission, the geriatricians provide geriatric specialty care, including, for example, evaluation for reversible causes of falls or urinary incontinence; investigation of the etiology of cognitive impairment; management of decubitus from a medical perspective; or recognition and treatment of malnutrition. The geriatrics fellow is responsible for the conduct of comprehensive geriatric assessment during the hospital stay. Medical housestaff are responsible for traditional primary medical care.

Consultants play an important role in the unit. Since about 50% of our frail elderly patients have a psychiatric co-morbidity, most commonly dementia, depression, or delirium, a liaison psychiatrist with board certification in geriatric psychiatry is an integral unit team member. The impact of psychiatric co-morbidities on medical care is manifest by such events as patient refusal to cooperate with radiologic tests, drug noncompliance, and falls. The co-morbidities of dementia and delirium result in an approximate doubling of hospital length of stay (5, 6). Thus, the presence of the geriatric psychiatrist not only improves quality of care, but may insure efficient care and reduce length of stay. Other specialists, including a geriatrics neurologist, geriatrics physiatrist, and a nutritionist, also participate on the unit team.

The unit is staffed by nurses from the Division of Geriatric Nursing with special training in geriatric nursing. The unit has one of the highest nursing-to-patient ratios in the hospital because the average patient carries a high score on the MEDICUS scoring system employed throughout The Mount Sinai Hospital to determine nursing staffing on individual units (6). In fact, the unit nursing care acuity is almost equal to that in the cardiac care unit.

Social care is critically important in the unit (7). Most hospitalized frail elderly have significant psychosocial problems that have an important effect on health care outcomes. The unit social worker has special training in geriatric social work. In contrast to the social worker on the traditional medical ward, the geriatrics unit social worker functions following a "screening" rather than "consultation" model, so every patient is seen by the social worker within 24 hours of admission to insure effective social counseling and efficient discharge planning from day one of admission. Because family members are often essential to the posthospitalization care of the frail elderly as caregivers or as case managers, the unit holds frequent family conferences. Housestaff are asked to participate in these family conferences and are often enlightened to discover the great efforts families are often required to provide to meet their frail elderly family member's health care needs. These conferences also assist in improving quality of care and reducing length of stay by facilitating discharge planning.

The Process of Geriatric Assessment in the Unit

Comprehensive and efficient acute geriatric care is provided through the process of geriatric assessment combined with traditional medical care. Comprehensive geriatric assessment is a method of geriatric care that employs the team approach to the evaluation and management of the hospitalized frail elderly with complex interdisciplinary health care needs (see box) and is accomplished through the use of an organized, efficient set of "instruments" to insure that the assessment process is structured and quantitative and does not prolong hospital length of stay.

Geriatric assessment in the unit is conducted by the unit fellow and is facilitated and organized by the *Handbook for Geriatric Assessment* (8). The admission comprehensive geriatric assessment is completed within 48 hours of admission

Essential Components of Comprehensive Geriatric Assessment

Physical Health
- geriatric medicine history, physical exam, laboratory tests; for example, gait/falls/mobility assessment, incontinence assessment

Functional Health
- activities of daily living
- instrumental activities of daily living

Mental Health
- cognitive assessment (dementia, delirium)
- affect assessment (depression)

Social Health
- economic assessment
- caregiver assessment
- health care proxy
- estate planning

and summarized by the fellow in a "Geriatric Assessment" admission note in the patient's medical record. The results of the assessment process are discussed with housestaff, students, and other team members.

Frail elderly patients may benefit from admission to the unit for inpatient comprehensive geriatric assessment when an outpatient assessment would require numerous clinic or office visits over the course of several weeks or months, during which time the patient might progressively deteriorate as a result of unresolved problems and be at great risk for further morbidity or even mortality. Thus, an important concept regarding admissions for "geriatric assessment" under Medicare is that of multiple diagnoses in frail elderly patients for whom the diagnostic sum is greater than its parts. That is, whereas no single diagnosis alone might justify the admission of an individual patient, a multitude of diagnoses might equal an "acute" admission because the sum of the complex problems results in a geometric increase in morbidity. Although obvious risks are associated with hospitalization, these might be outweighed by the benefits of a relatively quick and comprehensive evaluation of complex problems.

Medicare does not provide a diagnosis-related group (DRG) for geriatric assessment. Therefore, the performance of geriatric assessment under the Medicare Prospective Payment system must be an efficient and comprehensive process that does not prolong hospital length of stay. Although these patients clearly require hospital admission to the unit for geriatric assessment, they may not have traditional diagnoses normally employed by internists for acute care under Medicare. However, many DRGs of the Medicare Prospective Payment system can be employed for admitting these frail patients. In addition to the usual acute-care diagnoses, a number of DRG diagnoses are applicable, such as change in mental status, Alzheimer's disease or senile dementia, decubiti, urinary incontinence, sleep disorders, cachexia, malnutrition, or weight loss. Diagnosis alone is not the sole criterion for approval of admission. The most important aspect of a successful Medicare admission for "geriatric assessment" is the documentation in the admitting note of the medical record, which clearly explains the acuity of the patient's illness, particularly from an expert geriatric medicine perspective.

Is the Unit Cost-Effective?

Several research studies have demonstrated that geriatric assessment units provide high-quality comprehensive geriatric care while saving the health care system money (3). With proper targeting, geriatric assessment units clearly have the capacity to improve a variety of hospital outcomes, including reduction in mortality for patients when followed for up to one year. Much of the cost savings has come from a reduction in nursing home utilization during the year after admission to the geriatric unit.

However, the Mount Sinai unit is a mixed-use acute-care geriatric unit that functions to meet the needs of our local hospital health system. As with other special care units such as those for stroke or cardiac care, the actual cost effectiveness of this geriatrics unit has not been demonstrated. However, data on length of stay is available. In 1987, the average length of stay was approximately 28 days. Subsequent studies (7) revealed the important contribution of hospital "social stays" to total length of stay in the unit (Table 3). These studies demonstrated that a minority of frail elderly with prolonged hospital lengths of stay that included up to 70% alternate-level-of-care days markedly prolonged total length of stay on the unit. By 1989, the average length of stay had been reduced to approximately 16 days and now averages about 15 days. Major reductions in hospital length of stay were achieved through focused team efforts at discharge planning, including intensive social work intervention (7). These data are consistent with other hospital reports of length of stay for frail elderly patients in this age group (average age 83 years) who commonly have psychiatric co-morbidity and social problems (9). The decrease in length of stay achieved by the reduction in alternate-level-of-care stays and other mechanisms was estimated to save over $3 million per year in hospital costs. Thus, our hypothesis is that acute geriatric care in the unit provides a win-win situation: improvement in quality of care, accompanied by a reduction in hospital length of stay compared to an equivalent "control" group of hospitalized frail elderly given acute care on traditional medical wards.

TABLE 3
Summary Data: Length of Hospital Stay (LOS) for the Frail Elderly, Geriatric Evaluation and Treatment Unit Days, Mean ± SD

	LOS		
Pt group (no.)	Total	Acute	ALC
All unit pts (233)	27 ± 31	19 ± 20	—
Acute care only (150)	16 ± 16	16 ± 16	—
Acute care and ALC (83)	48 ± 38	24 ± 25	24 ± 26

ALC, alternate level of care ("social care")
Adapted from (7).

Education in Geriatric Medicine In the Unit

The unit serves as the primary site for training in geriatrics for housestaff from the Department of Medicine. In this model, housestaff play an integral role in the provision of primary acute care while learning the principles of geriatric medicine through the supervision and assistance of fellows and faculty of the Department of Geriatrics. The education of medical students is also an important function of the unit. A geriatrics rotation is required of all medical students attending the Mount Sinai School of Medicine. Approximately 20% of students receive their clinical training on the unit. In addition to significant didactic training, medical students learn to perform complete geriatric assessments on aged patients under the direct supervision of the unit geriatrics fellow. The unit has been demonstrated to be a successful site for geriatrics education, both improving clinical skills and increasing knowledge (10).

There are three components to the body of knowledge in geriatric medicine taught in the unit: (a) how normal development (aging) affects the practice of geriatric medicine; (b) the altered presentation of disease in geriatric patients; and (c) specific diseases and syndromes particularly prevalent in old age. Although the effects of aging on organ function begin, in general, around the age of 30 or 40, they usually do not become clinically significant until the age of about 75 or 80. This knowledge becomes critically important in the provision of acute care to patients over the age of 75.

Geriatric medicine encompasses diseases (such as Alzheimer's disease) and syndromes (such as falls) that occur almost exclusively in old age and are rare in traditional "middle age" medicine. These geriatric syndromes often have multifactorial, sometimes reversible, causes. Falls provide a good illustration (11). Falling is connected with a high mortality rate in the elderly. Approximately 20% of people over the age of 80 who fall and break their hip are dead within one year. In a young population, the most common cause of falling might be syncope. But the most common cause of falling in old age is simple deconditioning.

Teaching on the unit is provided by geriatrics fellows and attending physicians on a daily basis through bedside rounds and through formal talks and conferences. Specialists in geriatric psychiatry, neurology, and physiatry also make weekly specialty teaching rounds. A syllabus with articles on geriatric medicine from the *New England Journal of Medicine,* the *Annals of Internal Medicine,* the *Journal of the American Geriatrics Society,* and other geriatric medicine subspecialty journals, as well as traditional textbooks on geriatric medicine (12), expose housestaff to the literature of geriatric medicine and help prepare them for the questions on geriatric medicine in the American Board of Internal Medicine Certification Examination.

Clinical Research in the Unit

The unit has been successfully employed as a site for clinical research in acute geriatric care. Research on length of stay in the hospitalized frail elderly has demonstrated the significance of alternate-level-of-care or "social care" stays in prolonging total hospital length of stay of these patients and has demonstrated the critical importance of intense social work intervention to prevent lengthy social stays (7).

Studies of the impact of dementia on ethical decisions have demonstrated that the majority of acutely ill frail elderly medical patients and their families opted for resuscitation rather than forgo life-sustaining technologies, but that for the demented elderly, families tended to choose "do not resuscitate" orders more frequently for their demented family member than patients themselves might (13).

Studies of the impact of dementia on acute medical care in the frail elderly have demonstrated the interesting finding that, whereas the most common cause of admission to hospital for the frail elderly without dementia was, as expected, cardiovascular disease, the most common cause of admission to hospital for medically ill demented patients was infectious disease (6). These studies also demonstrated the impact of dementia on hospital length of stay and costs (**Table 4**) and the gross underreporting of dementia as a DRG diagnosis in medically ill patients (**Table 5**). Other studies have compared the utility of two assessment instruments in the evaluation of cognitive impairment in acutely ill hospitalized frail elderly patients (14).

Studies of malnutrition and immunologic function in the hospitalized frail elderly have shown that over 40% of patients admitted to the unit were malnourished, that the sensitivity of detection of malnutrition in these patients could be increased employing anthropometry, and that the rate of immunodeficiency in the unit population was high, 43% of patients demonstrating lymphopenia and impaired delayed skin test hypersensitivity (15). These data emphasize that malnutrition is the most common (though often unrecognized) cause of acquired immunodeficiency in the elderly (16).

TABLE 4

Effect of Dementia on Hospital Length of Stay (LOS), Geriatric Evaluation and Treatment Unit Days, Mean ± SD

	Patients without dementia	Patients with dementia	p
Total LOS	17.12 (2.67)	33.55 (35.03)	.001
No. of acute days	12.83 (9.73)	23.54 (26.82)	.005
No. of alternate-level-of-care days	4.29 (8.52)	10.01 (17.94)	.029
Assigned LOS for DRG	6.59 (2.65)	7.78 (2.70)	.011
Difference between actual LOS and mean DRG LOS	10.53 (12.33)	25.29 (34.46)	.003
Net hospital profit or loss*	−$3,331 ($7,286)	−$5,910 ($9,034)	.066

DRG, diagnosis-related group

* Hospital operating costs minus revenues.

Adapted from (6).

TABLE 5

Dementia and the Medical Records Database, Geriatric Evaluation and Treatment Unit

Dementia coding	% of all dementia cases employed by hospital for DRG reimbursement (N = 90)
Admitting diagnosis	3.3
Co-morbidity	31.1
Total	34.4

Adapted from (6).

The two oldest known patients with acquired immunodeficiency syndrome (AIDS) induced by human immunodeficiency virus (HIV) have been reported. In one case, a 92-year-old man suffered an HIV infection at the age of 87 from a transfusion (17). The other case was an 89-year-old woman with HIV-AIDS secondary to heterosexual transmission (18). These two cases emphasize the occult nature of HIV-AIDS in elderly patients with typical geriatric syndromes of dementia and cachexia.

Summary

Geographically based inpatient geriatric units are an increasingly common organizational approach throughout the world for the care of the hospitalized frail elderly with complex, multidisciplinary acute care needs. The unit provides comprehensive and efficient quality care to these patients by bringing together, in a geographically based unit, specialists from a multiplicity of disciplines to provide needed services in a coordinated manner. To accomplish its goals, the unit employs experts in geriatric medicine, nursing, social work, psychiatry, and other disciplines in a team approach to comprehensive assessment. The education of medical students, medical housestaff, and geriatrics fellows is a critical function of the unit. The unit also serves as a site for research in improving the care of the hospitalized frail elderly.

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The Phyllis and Lee Coffey Ambulatory Care Clinic:

Ten Years of Evolution in Treating Older Adults

Barbara Paris, M.D., Diane E. Meier, M.D., Jane Morris, R.N., Nurit Ginsberg, C.S.W., and Linda Weiss, M.P.A.

A tremendous need exists for outpatient facilities to address the complex medical and psychosocial problems faced by the frail elderly (1). Such patients are best served by an interdisciplinary team that addresses the multidimensional problems of aging and aims to preserve the functional independence of the patients in their community. Our goal was to establish a clinic that could provide such services by staffing it with an interdisciplinary team of professionals trained in geriatrics to provide a longitudinal model for patient care.

The team approach, a central principle of geriatrics, is a departure from the traditional doctor-centered medical model and is the single most important characteristic differentiating the geriatrics clinic from a standard medical outpatient clinic. Such an approach is necessary to meet the needs of the frail older adult patient, whose requirements frequently exceed the skills and resources of any single professional discipline.

After a review of the literature describing parameters for geriatric clinics, we set in place a clinic that we hope serves as a model for other institutions. The clinic is also a key component of the Department of Geriatrics and Adult Development programs associated with housestaff training, medical student education, and clinical research.

Demographics

Established in 1983, the Phyllis and Lee Coffey Ambulatory Care Clinic provides comprehensive care and consultative services to patients who are primarily 65 years of age or older, many of them frail. Over 42% come from the surrounding East Harlem neighborhood. The population served ranges in age from 64 to 107 years; the average age of clinic patients is 79 years. Eighty-three percent of patients are women; 41% are African-American, 26% are Latino, and 12% are white. Approximately 40% of our patients are cognitively impaired and 60% are functionally dependent. Many are living alone.

There are 10 to 12 new patient referrals per week from diverse sources, including the emergency room, hospital inpatient services, community agencies, private practices, and word of mouth (**Fig.**). Approximately 25 patients are seen per clinic half-day (for a total of about 80 patients per week in four clinic sessions, or 3,200 patient visits per year). The complex and multiple needs of the patients makes this low number of visits necessary; a visit may last as long as two to three hours, requiring the time and attention of several members of the team and thus prohibiting larger patient loads. It is hoped that these time- and effort-intensive preventive measures will save resources over the long term by reducing both the number and duration of hospitalizations and nursing home placements.

The most common diagnoses in the Coffey Clinic mirror those nationally for patients 65 years and older, according to the 1992 National Center for Health Statistics: hypertension, chronic heart disease, diabetes mellitus, and os-

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teoarthritis (2). These have not changed since Calvert and Koch's report of 1981 (3).

Ninety-seven percent of our patients are covered by Medicare; the 20% co-payment is charged on a sliding scale according to ability to pay, and 57% also have Medicaid insurance. The remainder pay for their visits according to a sliding fee scale determined by income and family size. No patient is turned away for lack of resources.

The Clinic Team

The clinic team has evolved into a core staff of over 20 health care providers. The medical staff on the clinic team includes a geriatrician chief, attendings in geriatric medicine, and 10 fellows in a two-year training program. Additional medical consultants in neurology, neuropsychology, gynecology, gait disturbances, urinary incontinence, and cardiology provide the clinic with their expertise once a week. The nursing staff includes three nurses with advanced education in geriatrics and a nursing assistant, supervised by the director of geriatric and rehabilitation nursing. There are three certified social workers and a supervisory social worker. Other support staff members include a patient care coordinator, a Spanish translator, a database coordinator, and ambulatory care registrars and supervisor.

Patients are assigned to a miniteam consisting of a fellow, a nurse, a social worker, and a data input person. The team meets frequently to ensure communication about each patient and to outline and implement care plans. The entire clinic staff meets biweekly to discuss the most complex cases. Ongoing meetings between team members, patients, and caregivers assure clarity of communication and permit all involved to work together toward shared goals. Two additional regularly scheduled bimonthly meetings facilitate this process: a team meeting of all clinic staff, and an operational group meeting of the clinic chief, the director of geriatric nursing, and the social work supervisor. The more specific roles of team members are as follows.

Attending physicians are responsible for administrative issues that arise during clinic sessions, for medical consultation with the fellows, nurses, and social workers, and for teaching medical students.

Fellows serve as primary care and consultation physicians for all clinic patients. Each fellow is assigned a panel of approximately 50 patients and follows those patients throughout fellowship training.

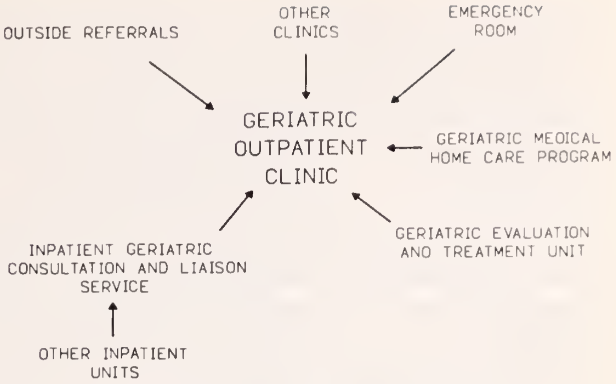
OUTSIDE REFERRALS
OTHER CLINICS
EMERGENCY ROOM
GERIATRIC OUTPATIENT CLINIC
GERIATRIC MEDICAL HOME CARE PROGRAM
GERIATRIC EVALUATION AND TREATMENT UNIT
INPATIENT GERIATRIC CONSULTATION AND LIAISON SERVICE
OTHER INPATIENT UNITS

Fig. Sources of patient referrals.

The clinic chief, the director of geriatric nursing, and the social work supervisor are responsible for general administration and policy of the clinic and for support and development of the team.

Geriatric nurses assess the patient's and the family's educational needs and teach preventive health measures (such as medications, nutrition, safe transferring from bed to wheelchair); they also provide highly skilled assessment and treatment of some of the most difficult problems of clinic patients, including pressure ulcers and bowel and bladder incontinence. The nurses also serve as liaisons to multiple community agencies.

Nursing assistants work under the immediate direction of the geriatric nurses and assist all members of the health care team. The nursing assistants' observations of patients are shared with other team members.

Social workers perform an initial psychosocial assessment of the patient and the family, evaluating coping capacities and available support networks and monitoring for depression, isolation, and elder abuse. Their role may involve crisis intervention and ongoing individual, family, and group therapy to help sort out conflicts arising from the needs of the older patient, including bereavement, anxiety over nursing home placement, elder abuse, and problems associated with Alzheimer's disease. Social workers also assist patients in identifying and acquiring community health and social services. The physician-nurse-social worker triad schedules frequent meetings to ensure timely communications about changes in the patient's status and appropriate adjustments of the care plan.

The neuropsychologist serves as an additional resource for patients' psychological and neuropsychological problems, available to discuss mental status abnormalities and questions about psychiatric diagnoses, psychotherapy, and family

Initial Outpatient Geriatric Assessments

Nursing Assessment
medical history
medications
nutrition
skin
functional status
mental status
mobility
health maintenance protocols

Medical Assessment
physical examination
advance directives
dementia
depression
osteoporosis
peripheral arterial obstructive disease
sleep disorders
urinary incontinence
substance abuse
elder abuse and neglect
sexual functions

Social Work Assessment
financial
psychological
family history
mood
caregiver burden

management with the fellow-nurse-social worker team.

The patient care coordinator screens and schedules all new patient appointments, assists with transportation arrangements for patients, makes reminder phone calls to patients prior to their appointments, and follows up on all patients who miss their appointments. An important role is monitoring the status of patients to identify those who are hospitalized, transferred to a chronic care facility, lost to follow-up, or dead.

The Spanish translator interprets for patients whose primary language is Spanish (30% of the clinic population). She also functions as a patient advocate. The staff relies on her expertise to identify the complexities of bilingual and bicultural communication. Patients often communicate information critical to their health status to the translator in the course of casual conversation in the clinic waiting area.

The database coordinator enhances communication between the department's various clinical services by assuring that up-to-date, vital information on medications, diagnoses, and health maintenance is available on the patient's medical record. Information is updated after each clinic visit.

The ambulatory care registrars, under the guidance of their supervisor, are receptionists in the clinic whose functions include making follow-up appointments for patients and medical record keeping.

The Team Approach to Patient Care

Geriatric assessment is the usual initial approach to gathering data on each patient and formulating a care plan. The goals of the assessment are

- Improved diagnostic accuracy
- Improved functional status or rehabilitation
- Improved efficacy of and compliance with medications
- Health promotion and disease prevention
- Better use of community support services
- Improved emotional status and sense of well-being
- Reduced use of acute and long-term care facilities

The average evaluation requires 3–5 visits to the geriatric clinic and results in a detailed and thorough medical, nursing, and social assessment, divided among the various members of the team (see **box**).

Each new patient is seen in an initial screening and assessment clinic staffed by the nurses, social workers, Spanish translator, and patient care coordinator. Validated assessment tools are used to evaluate functional status (4, 5), mental status (6, 7), mood (8), mobility (9), and caregiver stress (10). Additional data is gathered on medical history, skin care, nutrition, medications, finances, psychosocial circumstances, abuse and neglect.

Health maintenance protocols, based on the Report of the United States Preventive Services Task Force (11), are initiated, including blood and urine tests, electrocardiograms, tuberculosis screening, dental, vision, and hearing screens, mammograms, fecal occult blood testing, and immunizations. Laboratory and radiographic studies are ordered judiciously, with attention to expected yield and safety, but no patient is denied a thorough evaluation because of chronological age.

A patient is given a follow-up appointment with a physician within two weeks of the initial clinic visit. The physician then reviews all of the data collected in Management Clinic and performs additional assessments as individually indicated.

After the initial comprehensive assessment, patients may choose to return to their community physician for primary care or remain in the clinic. The vast majority continue to use the clinic as their primary health care provider.

Patients in the clinic are referred to other specialists as deemed necessary by the team. In addition to the many specialists on the clinic staff, patients have access to rehabilitation medicine, speech pathology, and numerous other medical and surgical sub-specialty clinics in close proximity to the Ambulatory Care Clinic. This "one-stop" approach to the multiple interacting problems of the aged contributes to patient compliance and involvement with their care and thus greatly increases the efficacy of care. This is advantageous to the patient, for it enables the team to oversee the patient care received from a variety of sources. For example, adverse drug reactions related to polypharmacy are more easily identified and averted. The team thus becomes the patient's advocate as he or she enters the larger health care arena.

Overall, 17% of clinic patients are admitted to the hospital annually. Most of these are admitted to the Geriatric Evaluation and Treatment Unit, staffed by attending physicians and fellows in the Department of Geriatrics and Adult Development. Both the inpatient and outpatient clinic staff meet monthly to discuss patients who have complex problems and prolonged or repeated hospital admissions. Clinic patients requiring hospitalization on other specialty units are followed up by the Geriatric Consult Service, also staffed by department faculty and fellows. Outpatients who become acutely ill when the clinic is not in session are referred to the hospital emergency room, and the Geriatric Consult Service is notified to make an assessment. Clinic patients who become homebound are referred to the Geriatric Medical Home Care Team for continuous care at home.

The Team at Work: A Case Study. An 81-year-old widow was referred to the clinic by a social worker at a local senior center for general medical care. The patient had been widowed for many years, her only son had died at the age of 30 years, and she had no other relatives. She was living alone and had little contact with the outside world other than one "friend" at the senior center where she ate lunch every day.

The patient arrived at the clinic escorted by a volunteer from the senior center. She was unkempt, with notably poor hygiene. At her first clinic visit, she was assessed by a fellow, a nurse, and a social worker. On initial evaluation, problems identified included malnutrition, unsteady gait, and confusion. For example, she could not do simple arithmetic, and she was unsure of the date. It was clear that she was incapable of handling her own finances, which she stated her "friend" took care of for her.

The team discussed the case, and the medical and psychosocial problems were immediately addressed. The patient was referred to a community agency that could provide home attendant services, with both nursing and social work supervision. Ambulette arrangements were initiated for her future clinic visits. Subsequently, a nurse and a social worker doing a home visit identified a need for heavy-duty cleaning services, evidence of financial mismanagement, limited food, and dirty clothing. A home attendant was placed in the home for six hours a day to assist the patient with cleaning, shopping, bathing, and meal preparation. The community agency also took the responsibility for future management of the patient's finances.

The patient continued to come to the clinic, where her medical and cognitive problems were further evaluated and treated. She remained stable in the community setting for eight years. At age 89, she required hospitalization and surgery for an acute bowel obstruction. After prolonged hospitalization, she was too frail and weak to return home and was transferred to an inpatient rehabilitation program. Finally, after many months of reconditioning, the patient's physical condition improved, and she was very anxious to go home. With the dedicated efforts of the team, in coordination with the community agency, this patient was discharged from the nursing home and reinstated in her own apartment. At age 90, she is happy and doing well.

Education and Training

The clinic is an important training site for fourth-year medical students and fellows. The educational objectives include:

Providing exposure to primary and consultative outpatient care of the older adult in a setting emphasizing continuity of care.

Learning the basic principles of case management and coordination of multiple services and providers in an outpatient setting.

Being comfortable and facile with the team approach to geriatric care by becoming aware of the skills and knowledge specific to the disciplines of nursing, social work, and psychology so that appropriate triage, referral, and communication will take place.

Becoming cognizant of the difficulties and frustrations that may confront the health professional in caring for the elderly and learning how to handle these feelings in a manner that does not interfere with appropriate high-quality patient care.

Learning the database of ambulatory geriatric medicine, including the approach to health maintenance, atypical presentation of disease, diseases characteristic of the elderly, problems of therapeutics and polypharmacy, risk-benefit analyses of diagnostic and therapeutic approaches to the older adult, and history and physical examination of the older person.

Being aware of the necessity for comprehensive functional assessment of the elderly patient for appropriate service assignment, prognostication, and protection of patient independence.

Becoming accustomed to working with patients' families and friends to maximize the well-being, autonomy, and strength of the patient.

Becoming familiar with the language and concepts relevant to the ethical dilemmas inherent in the care of the elderly, including problems of autonomy and paternalism, informed consent, and decisions to forgo life-sustaining therapy; specific training in how to approach discussions with patients about advance directives for health care.

Acting as teachers and role models for students from various disciplines rotating through the clinic, both in direct patient care and in leadership of educational and patient-family conferences.

Becoming familiar with the health-policy issues complicating the care of the elderly by observing first-hand the difficulties encountered by clinic patients and their families.

Learning the fundamentals of outpatient neuropsychological assessment and how to generate an appropriate differential diagnosis, diagnostic plan, and triage-referral pattern for the cognitive problems of the elderly.

Clinic Research

The clinic also serves as a research setting for investigators from the Department of Geriatrics as well as from the larger Medical Center community. Projects have included a time and intensity study for the Physician Payment Review Commission, a study of service needs of East Harlem Hispanic elderly, and the efficacy of initiation of health maintenance protocols by nurses over physicians. Results of these research projects have been presented at national meetings. Currently, an ongoing two-year study is assessing the utility of the New York State Health Care Proxy Law for our clinic population, many of whom have few social supports.

Ongoing Team Development Process

Over the past year, with the assistance of consultants from The Mount Sinai Hospital Department of Human Resources, our interdisciplinary team underwent an intensive review of its strengths and weaknesses, with the goals of maximizing good patient care, identifying and resolving interprofessional conflicts, enhancing communication skills, and increasing team member satisfaction in the work place. Three major areas of concern—the patient appointment system, the medical records and radiology retrieval systems, and the team meeting structure—were identified as requiring the establishment of problem-solving interdisciplinary working groups for further analysis. A significant outcome of this process has identified the need for an overall clinic administrator whose role would be to oversee clinic operations and keep the team focused on their common goal of quality patient care.

Conclusions

In summary, the Coffey Geriatrics Ambulatory Care Clinic is organized on an interdisciplinary model to provide comprehensive longitudinal care to the community's frail elderly, allowing them to maintain a maximal degree of functional independence. It also serves as a training site for housestaff and medical students to learn the skills needed to care for the frail elderly. To understand the growing challenges and complexities of providing such care, the clinic also serves as a forum for clinical research.

Acknowledgments

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Health Care for the Homebound Older Adult:

A Medical Model

Laura Di Pollina, M.D., Gabriel Gold, M.D., and Diane E. Meier, M.D.

More than 5 million elderly people living at home are functionally restricted because of mobility limitations; 1.6 million of these are severely impaired, and 300,000 live alone (1). Although physician house calls were commonplace before World War II, they have declined markedly over the past 50 years, representing only 1.7% of physician-patient contacts in 1979 (2). Because the homebound elderly are often in near-total isolation from health-care services, they generally have no physician and do not contact the health-care system until they are brought to the emergency room with a severe acute illness. After they are discharged from a hospital, they are at high risk of readmission because they are unable to make use of medical services outside their homes; not uncommonly, they are discharged to nursing homes.

In February 1991, the Department of Geriatrics and Adult Development at The Mount Sinai Medical Center initiated a geriatric medical home-care program (GMHCP) to provide comprehensive health-care team management, including physician visits to homebound elderly. The specific goals of the home-care program are to reduce emergency room visits and hospitalizations, obviate the need for nursing home placement, alleviate burdens on caregivers, provide home care to terminally ill patients, allow terminal patients to die at home rather than in the hospital if they so wish, generally improve the health and quality of life of the homebound elderly, and provide a teaching model for fellows, residents, and students.

Description of the Program

The program is staffed by a full-time nurse practitioner, a part-time (30%) social worker, and a part-time (60%) geriatric physician. Although the physician is fluent in both English and Spanish, the nurse and the social worker speak only English, and an individual available for Spanish translation when necessary has been identified. The program is also integrated with the Mount Sinai Home Care Agency, which provides other patient services, such as a nurse coordinator, physical therapists, occupational therapists, and escorts to unsafe areas.

Service components include medical care, nursing, social work, physical therapy, speech therapy, occupational therapy, podiatry, home health aides, laboratory services, X-rays, electrocardiograms, Holter monitoring, medical equipment, and supplies. A physician and a nurse coordinator are available by telephone 24 hours a day, seven days a week, to handle emergencies. Services are planned and coordinated by the program and the Mount Sinai Home Care Agency and are provided either directly or through contractual arrangements.

The initial evaluation is conducted by a board-certified geriatrician and a registered nurse and lasts approximately two hours. The initial social work evaluation is conducted at a later date (see **box**). Patients are seen by the physician every one to two months, or more frequently if necessary; nursing visits generally occur every

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one to two weeks, depending on the patient's needs (for instance, prefilling of medication dispenser, blood glucose monitoring, dressings, injections).

Patient Demographics

Since its inception in February 1991, the program has received 98 referrals and enrolled 46 patients who met admission criteria, as follows:

- Homebound as a result of physical frailty, cognitive dysfunction, or environmental barriers
- Lacks access to health care
- Resides within catchment area
- Willing to participate, has a support person available, and is able to summon help in case of emergency

Thirty patients are currently active. The patient population is mostly female and of advanced age (**Table**). Although whites predominate (52%), there is a large Hispanic group (30%), all of whom speak only Spanish; 17% are black. Most patients were referred from an outpatient setting (53%) because they were no longer able to keep their clinic or office appointments as a result of increasing disability; 20% were referred by community agencies as individuals isolated at home with no access to a physician's care; 18% were self-referred; and 9% were hospital inpatients referred through the Geriatrics Evaluation and Treatment Unit or the Geriatric Consultation and Liaison Service. All medical home-care program patients are Medicare beneficiaries, and 61% are enrolled in Medicaid.

Social Supports. Of the 46 patients enrolled in the program, 36 are widowed, 7 are married, 2 are single, and 1 is divorced. Most (48%) live alone, 15% live with their spouse, and 37% live with another family member, almost always a daughter. Many benefit from home health aide services (**Fig.**), and 54% of those living alone receive 24-hour home health aide support.

Functional Status. Patients are generally dependent in many activities of daily living (ADL), including feeding, dressing, grooming, transferring, bathing, and toileting; the average ADL score for this patient population is 5 (worst 0, best 12). Patients are generally not able to carry out any instrumental activities of daily living (IADL), such as traveling, shopping, meal preparation, housework, handling of finances, or self-administration of medications; the average IADL score of the patient population is 1 (worst 0, best 12). More than one-quarter of the patients (28%) are incapable of leaving their home, even with ambulation assistive devices or the assistance of another person.

Initial Patient Evaluation for Geriatric Medical Home-Care Program, Mount Sinai Medical Center

Medical and Nursing Evaluation

Complete history and physical examination
Housing and environmental assessment
Medication review (prescription and over-the-counter)
Performance Oriented Environmental Mobility screen (3)
Need for durable medical equipment (hospital bed, wheelchair, assistive devices)
Functional assessment, adapted from OARS (4)
Nutritional assessment
Folstein Mini-Mental State Exam (5)
Yesavage Mood Assessment Scale (6)

Social Work Evaluation

Psychosocial screen
Evaluation of caregiver stress by Burden Interview Scale (7)
Advance directives (living will, health care proxy)
Burial plan
Financial status and Medicaid eligibility

Health Status. Enrolled persons are frail and elderly and have many diseases and disabilities. The average number of medical diagnoses per patient is 7 and ranges from 2 to 14; the average number of medications per patient is 6 and ranges from 1 to 12. The prevalence of dementia is high (72%), and the average Folstein Mini-Mental State score for all patients is 15 (best score 30). The most common diagnoses include dementia, osteoarthritis, hypertension, coronary artery disease, congestive heart failure, hearing impairment, vision impairment, diabetes mellitus, anemia, cerebrovascular disease, and urinary incontinence. Of the 17 patients discharged thus far from the program, 50% died at home, 19% died in hospital, 19% were transferred to nursing homes, 6% were lost to follow-up after a hospitalization, and 6% recovered enough independence to return to ambulatory clinical services. A remarkable 73% of all deaths occurred at home (only 27% in the hospital), thus accomplishing one of the goals of the program, which is to pro-

TABLE

Age and Sex Distribution of Patients in the Health Care Program for the Homebound Elderly

	No. of pts (%)	Mean age (SD)	Age range (years)
Women	38 (83)	86 (10)	63–104
Men	8 (17)	83 (8)	66–91
Total	46 (100)	85 (9)	63–104

vide supportive and medical services to terminally ill patients who prefer to die at home rather than in the hospital.

Education of Physicians in Home Health Care

Medical students and residents generally receive no training in home care and, as a rule, their physician role models and mentors do not visit patients in their own home. The American College of Physicians (8), the American Geriatrics Society (9), and the American Medical Association's Council on Scientific Affairs (10) have all underscored the need for educating physicians in home care. Unfortunately, the lack of appropriate training sites and mentors is a major hindrance to this educational effort. The program is unusual in that the home-care team includes a faculty attending physician, thus providing an appropriate setting for the education of medical trainees in home care. All 10 geriatric fellows in Mount Sinai's program spend one month on a special rotation that includes home visits with the program, and many medical students have participated in the program as well. This teaching role is expanding, and by 1994 the program will be providing training to 30 medical students each year.

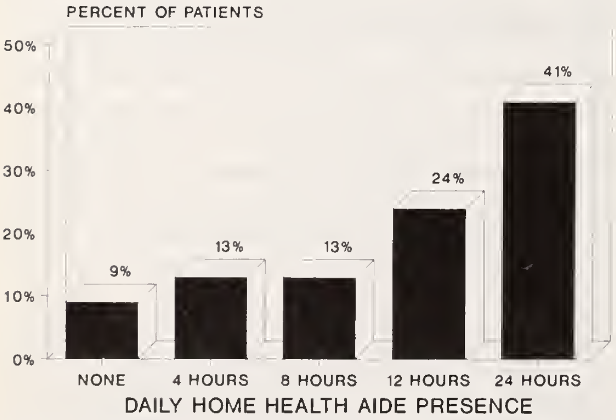

Fig. Proportion of patients of the Geriatric Medical Home-Care Program at Mount Sinai Medical Center receiving home health-aide services.

Illustrative Cases

Case 1. A 69-year-old black man was referred to the program by a medical primary-care clinic. He could only travel by stretcher and had not been seen in the referring clinic for over a year. Acute medical illnesses were requiring almost monthly emergency room visits.

The initial program evaluation revealed a patient who was bed-bound as a result of multiple strokes and who suffered from severe multi-infarct dementia, hypertension, pseudobulbar palsy with dysarthria and dysphagia resulting in recurrent aspiration pneumonias, and peptic ulcer disease that had led to multiple episodes of gastrointestinal bleeding and iron-deficiency anemia. The patient was fed through a gastrostomy tube, and his mobility was further impaired by a left lower extremity amputation above the knee. The patient's wife was overwhelmed by the task of caring for her husband and at a loss about where she could turn for help. The home-care program initiated a rehabilitation program that enabled the patient to regain enough strength and range of movement to be able to sit in a wheelchair. The program social worker addressed his wife's concerns. The patient has been under the care of the program for almost two years and, in that time, has visited the emergency room only once, to replace a dislodged gastrostomy tube. Occasional episodes of aspiration pneumonia have been successfully treated at home.

Case 2. A 90-year-old woman with multi-infarct dementia, chronic atrial fibrillation, hypertension, congestive heart failure, diabetes mellitus, a seizure disorder, and a history of multiple strokes had been receiving care at the geriatrics outpatient clinic but could no longer be transported there other than by ambulance. Control of her diabetes and hypertension deteriorated, and she was repeatedly brought to the emergency room for seizures. She and her family were adamantly opposed to nursing home placement. The case was referred to the home-care program.

The program reviewed diet and compliance with prescribed medication regimens with the patient's caretaker (her daughter), and after evaluation of the home situation, it was decided that the patient could remain home with appropriate support, including a 24-hour home health aide. The patient has been able to remain home, receiving continued medical care through the program. Weekly nurse visits were initiated to prefill the patient's medication dispenser, monitor her blood pressure and diabetic control, and counsel caregivers. Her phenytoin level has remained within the therapeutic range, and she has suffered no further seizures; her diabetes and hypertension are well controlled. The patient's course has been marked by several episodes of aspiration pneumonia, which were treated successfully at home by the program, and by another stroke, which led to a brief hospitalization. She has returned to her apartment and is receiving oral anticoagulant therapy with home monitoring of her prothrombin time.

Summary

The medical home-care program is a logical and indispensable addition to the comprehensive, multilevel geriatric care offered by the Department of Geriatrics. The home-care program enables the frail and homebound elderly to remain in their home environment and continue to receive comprehensive primary medical care and supportive services. It also serves as a valuable teaching site for medical trainees. Program evaluation through assessment of patient and caregiver satisfaction, estimates of costs of care, and frequency of hospitalization and emergency room visits are ongoing.

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Community Initiatives to Improve the Lives of Older Adults in East Harlem

JUDITH L. HOWE, M.A., M.P.A.

THE DEPARTMENT OF GERIATRICS AND ADULT DEVELOPMENT was established in 1982 at the Mount Sinai Medical Center in recognition of the need for an increased focus on the clinical, research, educational, and policy needs of a rapidly aging population. The overall goals of the department are to provide hospital-based and community-focused comprehensive health care; to conduct education and training for physicians, other health professionals, and the public; and to carry out aging-related research and policy studies.

Mount Sinai serves a broad catchment area, including East Harlem, which is an inner-city multiracial community comprised of lower-income and working-class residents. The elderly of East Harlem are particularly needy in a number of ways, including health care, social services, and housing. Since its founding, the department has actively reached out to the East Harlem elderly through a variety of approaches.

Background

As providers of a range of health care and other services to the older population of East Harlem, the department is challenged to work with its clients to achieve an optimal quality of life in the context of numerous difficulties. East Harlem's elderly face a multitude of problems as a result of financial hardship, shifting family and social support patterns, and inadequate access to needed services. Chief among the problems are inadequate living situations and incomes and difficulty in accessing health and social services. In addition, many older people have no involvement in family and community life.

East Harlem comprises the northeastern section of the borough of Manhattan, bounded on the south by East 96th Street, on the west by Fifth Avenue, on the east and north by the East and Harlem rivers. The total population of East Harlem is 108,408, with 11.6%, or 12,615, aged 65 or older in 1990, an increase from 10.5% in 1980 The ethnic composition of East Harlem is mixed According to 1990 census data, 38.7% of the total population is non-Hispanic black and 52.3% is Hispanic. Residents who speak little or no English constitute almost 13% of the population (1)

Thirty-four percent of those 65 and older living in East Harlem are below the poverty line according to 1990 census figures. In 1986 the median household income in East Harlem ($8,305 was only 41.5% of the city's median ($20,000). For older residents living in housing owned and managed by New York City, the median income was even lower, those on public assistance having a 1986 median income of only $4,428 (1).

The health status of the East Harlem elderly is worse than that of other older people in New York City, as measured by higher mortality rates. There is excess mortality resulting from conditions that are greatly influenced by the physical and social environment and inadequate access to health care, such as pneumonia and influenza, diabetes, and homicide. Also, compared to other older people in New York City, most East Harlem elderly have chronic conditions that make using public transportation difficult or impossible for them, thus increasing their isolation (2).

A 1989 report on primary care in East Harlem (3) found that the primary-care needs most lacking for older people are mental health services, home care and transportation services,

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and coordination of health care. The report recommended that steps be taken to integrate physical and mental health services with other services such as day care, home care, transportation, housing, senior centers, settlement houses, and religious institutions.

Departmental Community Outreach Programs

Since its establishment in 1982, the Department of Geriatrics has developed a number of programs geared to serving the needs of the older residents of East Harlem:

The Phyllis and Lee Coffey Outpatient Geriatrics Clinic serves approximately 700 patients in continuing primary care, most of whom live in East Harlem, Central Harlem, and other nearby communities.

The Geriatrics Home Medical Care Program provides comprehensive health services and management to homebound older people in East Harlem who have no other access to medical care.

The Well Elderly Program, in conjunction with the Senior Division of the 92nd Street Young Men's-Young Women's Hebrew Association, provides year-round health promotion and disease prevention services.

The Elder Abuse Assessment and Assistance Program provides direct service to individuals and families, as well as consultation, training, and resource materials to health care professionals at The Mount Sinai Hospital and in the community.

The Hunter College–Mount Sinai Geriatric Education Center offers ongoing training programs for community health professionals in the prevention, treatment, and diagnosis of disease.

The Alzheimer's Disease Research Center (ADRC), jointly sponsored by the Departments of Psychiatry and Geriatrics at Mount Sinai Medical Center, offers community education and outreach programs and support groups for patients, family members, and caregivers. Recently, the ADRC began working with a group of East Harlem senior centers to establish an educational program for seniors and staff regarding Alzheimer's disease. This program will also assess the prevalence of Alzheimer's disease among the Hispanic elderly in East Harlem, including follow-up treatment at Mount Sinai when indicated.

Project Linkage

In response to the department's concern for a comprehensive approach to the multitude of problems facing not only the elderly, but East Harlem residents of all ages, funding was sought to assist the department in assessing the feasibility of developing shared housing for older people in East Harlem. A unique model was envisioned, one which incorporated housing, after-school care for latchkey children, intergenerational programming, and health services.

The objectives of the program, called Project Linkage, are:

To increase the availability of affordable housing for low-income, elderly residents of East Harlem

To expand the availability of after-school care for East Harlem children aged 5 through 12

To provide meaningful roles for older people through intergenerational programs and activities shared with residents of the project

To improve access to health care services

In 1991 the department received a one-year grant from The New York Community Trust for a study to assess the feasibility of developing shared housing for the elderly, coupled with after-school programs for children, intergenerational programming, and health care services. A study aided by the Dept. of Community Relations, a consultant team, a projects advisory committee, and focus groups of East Harlem elderly residents found Project Linkage feasible.

In early 1993 a Mount Sinai team solicited capability statements from East Harlem community-based organizations interested in serving as cosponsors with Mount Sinai in developing and operating Project Linkage. After a systematic review process, a partnership was formed with the Community Association of the East Harlem Triangle, the Union Settlement Association, and the Greater Emmanuel Baptist Church to sponsor housing for the elderly under the HUD section 202 program. The respective boards of directors of all organizations endorsed the project and agreed to the conditions of sponsorship. The management team, consisting of representatives from the participating organizations, as well as a housing consultant and an architect, selected a site on East 118th Street between First and Second Avenues and developed an application for HUD section 202 financing.

Certain elements of the original model were modified to conform to strict HUD guidelines on design features and financing. For instance, whereas the feasibility study proposed a building of 50 studio apartments, the planned building has 70 one-bedroom apartments because of economies of scale.

Project Linkage is based on a shared housing model designed to facilitate communal living and the formation of informal support networks, while allowing for residents' privacy. Each apartment will have its own living room and kitchenette; in addition, each cluster of five or six apartments will have shared living and dining space to promote interaction among residents. There will also be common space for intergenerational activities, after-school programs, social programs, and health visits and screenings.

One strength of the model is the availability of on-site health and mental health services provided by the Department of Geriatrics and the Union Settlement Association. A consultation and examination room will be available on the first floor for health screenings and visits. Initially, residents will be healthy and independent, but the model will encompass "aging in place" as residents grow older. Successful aging in place is dependent on such factors as the availability of assistance from an informal support system and access to formal health and social services. Project Linkage meets both these requirements: the housing arrangement is such that the formation of natural helping networks is encouraged, and residents as they age will continue to have access to the continuum of health and social services provided by Mount Sinai and Union Settlement.

The full range of medical services along the care continuum from independence to dependence offered by the Department of Geriatrics and Adult Development and The Mount Sinai Medical Center will support Project Linkage residents as they age. These include:

- Health education and health promotion programs
- Specialized outpatient primary care
- Referral to the many specialized clinical services at The Mount Sinai Hospital as needed (for instance, rehabilitation, radiology, osteoporosis, and geropsychiatry)
- Admission to The Mount Sinai Hospital specialized geriatrics inpatient unit, which focuses on the treatment of frail older persons
- For those East Harlem residents admitted to other units at The Mount Sinai Hospital, the services of the Geriatrics Consultation Service
- The Geriatrics Home Medical Care Program for those older individuals unable to travel to the hospital for care

In early October 1993 The Mount Sinai Hospital was notified by HUD that it had received a grant of almost $5.8 million to proceed with building section 202 housing for Project Linkage at the selected site.

Conclusions

The department has provided a range of health services to the East Harlem elderly during its first ten years. In addition to direct delivery of service, it has played an important role in developing community-based programs in East Harlem.

Working coalitions between large health care institutions and community organizations are often difficult to develop and sustain. For instance, in 1986 the Geriatrics and the Community Medicine departments spearheaded the formation of a coalition of about 13 East Harlem agencies to coordinate health and social services for frail older people, called the East Harlem Living at Home Program. The coalition, however, struggled to meet the program goal of targeting older people at risk for institutionalization and providing coordinated services, in large part because of staffing problems and difficulties in maintaining the coalition structure.

In Project Linkage, great care was taken to build a coalition made up of committed and strong member organizations, with Mount Sinai, through the departments of Geriatrics and Community Relations, playing a more active organizational role in program development and management.

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Education, Clinical Services, and Research On Treating Older People

Management of Geriatric Disorders

Practical Pharmacology for Older Patients:

Avoiding Adverse Drug Effects

Judith Ahronheim, M.D.

Older individuals take larger numbers of prescription drugs than do their younger counterparts (1, 2). According to national databases, the number of adverse drug events (ADEs) increases with age (2). This is partly (4, 5), though not entirely, related to increased drug exposure, for the older the patient, the more likely the ADE will be serious (3). Principles of geriatric pharmacology have been widely reviewed (6–8), and, to prescribe appropriately, the physician should keep these principles in mind. This paper highlights various factors that contribute to the geriatric patient's increased susceptibility to ADEs.

Altered Pharmacokinetics

With advancing age come alterations in pharmacokinetics—that is, the impact of distribution, metabolism, and elimination of drugs on the timing of a drug's effects.

Renal Function. The most consistently described change is due to an age-related decline in renal function. On the average, glomerular filtration rate declines approximately 50% between the ages of 20 and 70 years (9, 10). This degree of renal functional decline from a normal baseline does not produce illness; however, it may be inadequate for the elimination of active substances given exogenously, and toxic levels of drugs may occur if doses are not properly adjusted. This is especially important when the drug has a narrow therapeutic index (therapeutic-to-toxic ratio). Renally eliminated penicillin has a wide therapeutic index and only rarely produces dose-related toxicity, so age-adjusted dosing is considered optional. In contrast, aminoglycoside antibiotics, such as gentamicin, produce nephrotoxicity when only slightly supratherapeutic doses are given. It is thus essential that the dose of the latter group of drugs be carefully adjusted according to the patient's renal function. Other important renally excreted drugs with a narrow therapeutic index include digoxin, vancomycin, and imipenem. It has been our experience on the Mount Sinai Geriatrics Consultation Service that the most common prescribing error on medical and nonmedical wards is the overdosing of renally excreted antibiotics with a narrow therapeutic index.

Not all geriatric patients have significant declines in glomerular filtration rate. In fact, longitudinal studies have shown that at least one-third of the elderly maintain stable renal function for a period of years (11). Thus, age alone is not predictive of the degree of functional renal decline, and some other predictor must be used. The clinician is most likely to measure renal function using standard laboratory tests, such as creatinine clearance or serum creatinine. However, because muscle mass declines with age, serum creatinine, a reflection of muscle mass, may fail to reflect a significant age-related decrease in creatinine clearance. Under the best of circumstances, it is cumbersome to collect an accurate 24-hr urine specimen for creatinine clearance determination; for many elderly patients, collecting such a specimen may prove impossible in practice. A popular formula used to estimate creatinine clearance is (12):

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$$\text{Creatinine clearance} = \frac{\text{weight (kg)} \times (140 - \text{age})}{72 \times \text{serum creatinine (mg/dL)}}$$

For women, multiply result × 0.85

Because of the wide variation in renal function among the elderly, this formula may both overestimate and underestimate actual renal function. Since such a formula assumes that renal function is stable, it cannot be relied upon in the acutely ill, whose renal function may change daily. Furthermore, in the debilitated elderly, this formula often overestimates actual creatinine clearance by as much as 20% (13), presumably because the correlation between lean body weight and muscle mass is altered. However, predictive formulas have practical applicability in certain situations. For example, in an acutely ill hospitalized patient who requires a drug with a narrow therapeutic index, it is helpful to calculate the dosage based on estimated renal function until serum drug levels can be obtained and the dosage can be readjusted accordingly.

Loading Dose and Maintenance Dose. Note that the loading dose for drugs does not necessarily have to be age-adjusted. Although the pharmacodynamic effect of many drugs may be enhanced in late life (see below), toxicity based on altered pharmacokinetics develops only after repeated dosing. When a therapeutic effect is urgently needed, as in serious infection, adequate serum and tissue levels must be attained. This is achieved if a non-age-adjusted loading dose is given, and dose-related toxicity is avoided if the maintenance dose is tailored to the patient's ability to eliminate the drug.

Hepatic Function: Oxidation and Conjugation. Certain changes in hepatic function also occur with advancing age. Those that affect drug handling include decreased hepatic blood flow (14) and altered activity of oxidative enzymes involved in drug metabolism (15). Decreased hepatic blood flow reduces the efficiency with which the liver can handle drugs that present for metabolism. However, there is no unanimity of opinion regarding age-related hepatic function (15–17), and there are no simple measures of these changes in hepatic processes. Furthermore, it has been difficult for pharmacokinetic studies to home in on individual hepatic processes involved in drug handling, since drug metabolism depends on the coordination of complex processes in a number of organ systems. In general, it has been shown that hepatic oxidation ("phase I metabolism") may decline somewhat with age, whereas hepatic conjugation ("phase II metabolism") does not.

Some oxidated metabolites are pharmacologically active, and they are also excreted renally. The combined effect of this is that the action of many hepatically oxidized drugs can be markedly prolonged in older individuals. For example, flurazepam (Dalmane), a benzodiazepine hypnotic, is oxidized to dealkylflurazepam, a renally excreted metabolite that is pharmacologically active. Owing to the activity of this metabolite, the half-life of one 15-mg dose of flurazepam may be twice as long in the overtly healthy elderly as in younger adults, averaging about 120 hr in elderly women and 160 hr in elderly men (18).

The cytochrome P-450 system, the major source of hepatic oxidative enzymes, is affected by exogenous substances, including a wide variety of drugs. These substances may either inhibit or stimulate the enzyme system, producing an alteration in the drug's duration of action. There is controversy over whether these modifications (enzyme inducibility or inhibition) are altered in late life. However, enzyme inducibility and inhibition is responsible for many drug-drug interactions, and the elderly patient's increased exposure to drugs increases the likelihood of such interactions (5).

Nonoxidative Processes. Many drugs are metabolized in the liver by conjugation with a new molecule. These nonoxidative processes are not significantly altered with age; furthermore, the resulting metabolites tend to be inactive. Thus, drugs metabolized by hepatic conjugation do not generally have an increased half-life in elderly patients. This is the case for oxazepam and lorazepam, which are themselves active metabolic products of other benzodiazepines.

Volume of Distribution. The volume of distribution (Vd) for drugs may be altered with age. The Vd is the hypothetical space in which the total amount of drug in the body would distribute to achieve the same concentration in plasma. The Vd is calculated by dividing the total amount of drug by the concentration that amount has achieved in plasma. The ratio of fat-to-lean body weight increases with age, more in women than in men. As a consequence, the Vd for fat-soluble drugs increases with age, and steady-state concentrations for lipid-soluble drugs, such as the benzodiazepines, may be reached later than expected. If the patient continues to take a drug like flurazepam, which has an increased Vd (in addition to slowed oxidation and a renally excreted active metabolite), or increases the dose, delayed toxicity may occur. The patient or physician may fail to recognize that an adverse effect is due to the drug, which might have been initiated two weeks earlier. Conversely, the volume of distribution for water-soluble drugs tends to decrease with age. As a consequence, the peak effect of a substance like alcohol, which distributes in water, tends to occur earlier than expected.

Protein Synthesis. Protein synthesis is impaired with age (19). Serum levels of albumin tend to remain in the normal range among healthy elderly persons, but a number of acute and chronic illnesses may rapidly produce hypoalbuminemia (20), and this condition is probably more likely to occur in the elderly patient with diminished protein intake (21). This may have implications for prescribing drugs that are highly protein bound. If a drug is highly bound to albumin, a decrease in albumin leads to an increase in the proportion of drug that is unbound (free), the active fraction of the drug. Free drug travels more rapidly to the liver and kidney than bound drug and, therefore, is also more swiftly eliminated; thus, in the presence of hypoalbuminemia, enhanced activity of the drug is unlikely to last a significant amount of time, if at all. However, the development of hypoalbuminemia may become important when one tries to interpret serum levels of drugs highly bound to albumin (22). Routine clinical laboratory determinations measure total drug, which includes both the bound and free fractions. Therefore, a patient who is hypoalbuminemic may have a subtherapeutic to normal serum level of total drug, but a normal to supratherapeutic level of free drug. In such a situation, the clinician might mistakenly increase the dose of the drug based on the reported level of total drug. If a highly bound drug also has a narrow therapeutic index, as does, for example, phenytoin, a slight dose increase could lead to unexpected toxicity.

A number of drugs have affinity not for albumin but for alpha-1 acid glycoprotein (AAG). This protein is an acute-phase reactant and, in contrast to albumin, tends to increase rather than decrease with age and illness. AAG is not determined by routine laboratory studies, fluctuates greatly, and therefore plays a limited role in clinical decision making. However, knowledge of AAG may help to explain peculiarities of dose and effect. For example, following a myocardial infarction, AAG levels tend to increase, leading to an increase in total serum levels of lidocaine, a drug commonly used in the peri-infarction period. Because lidocaine is extensively bound to AAG, free lidocaine levels would decrease, so total serum levels might overestimate the potential clinical effect of the drug (23). There is insufficient information on the degree to which free levels correlate with clinical effect, and this interesting phenomenon awaits further study. However, it is important to recognize this phenomenon when interpreting total levels of highly bound drugs in the elderly.

Altered Pharmacodynamics

Pharmacodynamics refers to the specific action of the drug at the tissue level. The pharmacodynamic effect of a given drug may be enhanced or decreased in the elderly, owing to physiologic and pathologic changes in both target and nontarget organs. For example, beta-receptor sensitivity may be reduced in late life, leading to diminished response to both beta agonists and antagonists (24). Although it has been reported that elderly patients achieve less hypotensive response to beta blockers than do younger adults (25), another study revealed that metoprolol was more effective among elderly than among many younger cardiac patients in preventing recurrent myocardial infarction (26). Both inadequate hypotensive response and enhanced cardioprotection could perhaps be explained by other factors, however, so the clinical implications of impaired beta-receptor sensitivity are not known.

More commonly, pharmacodynamic effects of drugs are enhanced—or appear to be enhanced—in older patients. Important examples are drugs that affect the central nervous system, which are a common cause of confusional states in the elderly (4). This may be due to the high prevalence of underlying Alzheimer's disease, other central nervous system lesions, or age- and disease-related alterations in neurotransmitter concentrations. The patient may be cognitively normal until exposed to the offending agent because the potential central nervous system deficits are subclinical. Thus, the clinician should be alert for the development of confusional states in the elderly when a variety of drugs are given.

Drugs that can cause confusion include:

- Any sedative
- Any hypnotic
- Antidepressants
- Anticonvulsants
- Centrally acting antihypertensives
- Lidocaine
- Digoxin
- Isoniazid
- Corticosteroids
- Theophylline
- Anticholinergic agents
- Nonsteroidal anti-inflammatory agents
- Histamine-2 blockers
- Any drug until proven otherwise

It is not always possible to determine when an enhanced effect is related to altered pharma-

TABLE
Pharmacodynamic Alterations in the Elderly

	Drug	Possible outcome or side effect
Alteration		
Impaired baroreceptor function; venous insufficiency	Diuretics; tricyclics; methyldopa; others	Orthostatic hypotension
Impaired counter-regulatory mechanisms	Hydralazine	No reflex tachycardia
Altered temperature regulation	Phenothiazines	Hypo- or hyperthermia
Increased ADH secretion	Chlorpropamide; others	Hyponatremia
Decreased androgenic hormones (males)	Digoxin; spironolactone	Gynecomastia
Underlying disorder*		
Atrophic gastritis	Aspirin; NSAIDs	Gastric hemorrhage
Immobility; cathartic bowel	Many	Constipation
Dementia	Many	Confusional state
Sinus or AV nodal disease	Digoxin; verapamil	Bradycardia
Venous insufficiency	Nifedipine	Edema
Unstable bladder	Diuretic	Incontinence
Prostatic hyperplasia	Anticholinergics; tricyclics; disopyramide	Urinary retention
Parkinson's disease	Metoclopramide; neuroleptics	Parkinsonian symptoms

* May be subclinical.
Adapted with permission from (27).

codynamics or pharmacokinetics. To prove that there is enhanced sensitivity at the tissue level, one would have to demonstrate an enhanced effect in the face of an ordinary serum or, more precisely, tissue concentration of the drug. In many cases, the patient's seeming overreaction might well be related to supratherapeutic levels of the drug caused by diminished elimination. However, clinical experience has shown that adverse drug events often manifest themselves in specific ways in the elderly patient. Examples of drugs and their potential effects, based on apparent altered pharmacodynamics, are listed in the Table.

Summary

Older patients experience adverse drug events more frequently than do younger adults, and they experience them in unexpected ways. The heterogeneity of the geriatric population leaves the investigator with a great deal of uncertainty and the clinician with little reliable guidance based on clinical investigations. Although few generalizations can be made, it is safe to say that at least a subgroup of patients exhibit one or more physiologic or pathologic alterations that can lead to unanticipated drug response. It is essential for the prescribing clinician to be mindful of the vulnerability of this population. Prescribing should be judicious and, in general, conservative, with an eye on the patient's specific vulnerabilities.

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Evaluation and Management of Urinary Incontinence in Older Patients

Perry Starer, M.D.

Urinary incontinence occurs in 10% to 43% of elderly individuals aged 65 years or older living in the community (1–6) and 36% to 62% of elderly patients living in long-term-care facilities (7–10). Complications from urinary incontinence include skin breakdown, infection, and loss of self-esteem (11). The economic cost of urinary incontinence is high because of its many ramifications, including laundry, disposable diapers, medical complications, and institutionalization (12, 13). The social and emotional cost is also high, though more difficult to quantify, contributing to isolation, embarrassment, and frequent institutionalization (13). Successful treatment of incontinence may provide many older individuals with an improved quality of life and an opportunity to remain independent in the community.

Management of urinary incontinence perplexes and distresses both patient and clinician. Appropriate diagnostic and therapeutic interventions are often overlooked. Instead, diapers or catheters are applied and the problem is concealed (14). To select the appropriate treatment for an elderly incontinent patient, the cause of the urinary incontinence needs to be determined.

Patterns of Abnormality

Urinary incontinence is the initial manifestation of a variety of underlying pathologic processes. Incontinence can be classified by the following patterns of presentation: detrusor instability; overflow incontinence: urinary retention and detrusor-urethral sphincter dyssynergia; stress incontinence: sphincter insufficiency; functional incontinence; and iatrogenic incontinence (14). The most common urodynamic abnormality in incontinent geriatric outpatients (15), detrusor instability (with or without intact detrusor contractility), is also the most common cause of potentially correctable urinary incontinence in nursing home patients (16). However, there may be multiple contributory factors (17).

Neurourology. The central nervous system receives afferent impulses from stretch receptors in the bladder wall during filling (18). The concept of a "cortical inhibitory area acting on a sacral reflex arc" may be an oversimplification (19). The sacral micturition reflex is influenced by facilitatory and inhibitory areas located at different levels of the neural axis (19). Diencephalic and brain stem areas controlling the micturition reflex include a cerebral inhibitory region, a hypothalamic facilitatory area in the mammillary region of the posterior hypothalamus, a midbrain inhibitory area localized bilaterally in the tegmentum lateral to the central gray matter at the caudal superior collicular level, and a pontine facilitatory area localized bilaterally in the dorsal tegmentum at the isthmus level immediately ventral to the lateral angles of the periventricular gray matter (19, 20).

Detrusor Instability. Detrusor instability, the occurrence of uninhibited detrusor contractions (14), is a common urodynamic finding among elderly incontinent patients (8, 21–24). Involuntary, uninhibited detrusor contractions may be produced either by increased afferent impulses to the central nervous system due to local disorders in the bladder or the urethra or by a neurologic disorder affecting the inhibitory nervous

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pathways from cortical and subcortical centers (18). Provocative upright cystometry is helpful in diagnosing involuntary contractions not provoked in the supine position (25). The symptoms of urinary frequency and urgency may occur in the presence of detrusor instability without being associated with urinary incontinence (12).

Detrusor instability may be associated with bladder outlet obstruction (26–28), but there is no correlation between the severity of obstruction and the presence of instability (29, 30). Detrusor instability is reversible in the majority of patients undergoing surgery for bladder outlet obstruction (28, 30). Detrusor instability may also be found in women with stress incontinence (15, 31). Since detrusor instability has been reported as being present in nonincontinent subjects (15, 32, 33), the clinical significance of this entity becomes unclear. An elderly patient with involuntary bladder contractions may be continent (32, 33), but following a cerebrovascular accident, the combination of impaired mobility and involuntary contractions may lead to urinary dysfunction.

Overflow Incontinence: Urinary Retention. Urinary retention may occur secondary to bladder outlet obstruction or poor bladder contractions. Medications may cause urinary retention, and anticholinergic agents can inhibit bladder contractions. Alpha-adrenergic stimulating agents can increase outlet and urethral pressure. A patient's inability to voluntarily contract the bladder during cystometric testing may be a result of discomfort during the procedure, leading to an incorrect diagnosis of a noncontractile bladder. Normal patients may be unable to produce a bladder contraction during cystometric studies, even though no abnormality exists (34). An inability to urinate in the presence of other people could be mistaken for bladder dysfunction.

The choice of therapy depends on the cause of retention. Surgical treatment may be indicated in the setting of bladder outflow obstruction. Most patients experience an improvement in prostatic symptoms following transurethral resection of the prostate for benign prostatic hypertrophy (35). Since the symptomatology of detrusor instability without infravesical obstruction is similar to the symptomatology of prostatism, it is important to obtain objective evidence of infravesical obstruction before surgery (30, 36, 37). It is difficult to use the symptoms of prostatism as an index of whether obstruction has been relieved because symptomatic improvement postoperatively may be related to a decrease in detrusor instability (36). The results of prostatectomy are poor when done in patients within a year following a cerebrovascular accident (38). Postoperative urinary incontinence in patients with cerebrovascular disease may be due to detrusor dysfunction or reduced cerebral control of micturition (39).

Even though bethanechol chloride, a cholinergic agent, is pharmacologically active, it has not been shown to be effective in promoting bladder emptying (40). Crede's maneuver (the application of steady suprapubic pressure over the full bladder in a caudal direction) is an inefficient method of bladder emptying for most patients (41). Although prostatectomy is the currently accepted treatment of benign prostatic hyperplasia, the role of pharmacologic therapy is being investigated (42). The clinical efficacy of alpha-adrenergic blockers is related to relaxation of the smooth muscle component of the prostate (42). The alpha-adrenergic blocker phenoxybenzamine may have a place in the management of patients with symptoms attributable to bladder outflow obstruction, especially when surgical treatment needs to be delayed (43, 44). Terazosin, a long-acting selective alpha-1 blocker, is a safe and effective therapy for symptomatic benign prostatic hyperplasia (45). Treatment of benign prostatic hyperplasia with finasteride, a competitive inhibitor of 5-alpha-reductase, results in decreased serum dihydrotestosterone concentrations, a decrease in prostatic volume, and an increase in urinary flow (46).

Overflow Incontinence: Detrusor-Urethral Sphincter Dyssynergia. Detrusor-external sphincter dyssynergia is the inappropriate contraction or failure of relaxation of the external urethral sphincter during detrusor contractions (47, 48). This discordant micturition reflex can elevate the residual urine (49). The normal relationship between the detrusor and the external sphincter is disrupted after spinal cord injury interrupts the pathways connecting the pontine mesencephalic and the sacral micturition centers (48, 50).

Some investigators have hypothesized that detrusor-sphincter dyssynergia is an abnormal flexor response of the perineal musculature to bladder contraction (51), whereas others have proposed that external sphincter dyssynergia is an exaggerated continence reflex (increasing external urethral sphincter electromyographic activity with bladder filling) (52). The loss of continuity between the sacral cord pudendal and vesical motor nuclei and the supraspinal micturition centers results in the loss of appropriate inhibition of the pudendal motor nucleus during a detrusor contraction (52). Beclofen, an antispastic drug, decreases external urethral sphincter resistance and reduces residual urine in with patients spinal cord injury (49).

Stress Incontinence: Sphincter Insufficiency. Stress urinary incontinence is the involuntary loss of urine caused by an increase in intra-abdominal pressure but not by contraction of the detrusor muscle (53). It has been described as the most common cause of urinary incontinence in women (53). Although a surgical procedure is often recommended as treatment, anatomic stress incontinence is not present in all incontinent women, who, in turn, may not benefit from a surgical procedure (54). Before surgical therapy is recommended for incontinent women, it is important to determine the etiology of their urinary dysfunction.

Although the evaluation of the patient begins with a history of urinary complaints, the patient's description of symptoms may be misleading. In a study by Glezerman et al. (55), stress incontinence was diagnosed in 81.6% of 130 women complaining of urinary stress incontinence, and it was concluded that history alone would not have been an appropriate indication for surgery. The history should not be solely relied on in determining therapy for incontinence. Urodynamic evaluation may reveal unsuspected bladder dysfunction. An assumption cannot be made that all women have stress incontinence, especially those patients with neurologic disease.

The significance of the presence of detrusor instability in the setting of stress incontinence needs to be understood when considering surgical therapy. Stress incontinence and detrusor instability should be differentiated in the evaluation of urinary incontinence. In a study of 309 elderly incontinent patients, pure stress incontinence was rarely found (22). Detrusor instability is often the cause of leakage of urine associated with coughing or laughing (22). In some incontinent women, both stress incontinence and detrusor instability may be present (53). Drutz and Mandel (56) reported that, of women with a history suggestive of pure sphincter weakness incontinence, over 20% had unstable bladders. Both stress incontinence and urgency incontinence may be cured by surgical elevation of the vesical neck (53). Although there are reports of postoperative failures in women with detrusor instability (57), the presence of detrusor instability in a patient with stress incontinence is not predictive of a poor operative result (31, 53); on the other hand, patients with detrusor instability who do not have anatomic stress incontinence may not benefit from surgery. A small number of patients without stress incontinence may be detected by urodynamic and radiographic studies (31). Many older women may be physically ineligible for surgery or fearful of operations (58).

Any of the symptoms of detrusor instability may be confused with anatomic stress incontinence, since an increase in intra-abdominal pressure may precipitate an uninhibited detrusor contraction. Since treatment plans may differ, it is important to differentiate between them. Although urine loss associated with coughing may be visually demonstrated in patients with stress incontinence, a spontaneous detrusor contraction can occur 5–15 sec after a cough (53). Since detrusor instability may not be detected in the supine position, it is necessary to perform cystometry with postural change and with coughing (57). Because it is difficult to classify the etiology of urinary incontinence based on symptoms alone, cystometric studies have been recommended in the evaluation of patients prior to surgical treatment for stress incontinence (23, 59). This is especially important in the evaluation of incontinent women with neurologic disorders, who may have detrusor instability alone or in addition to anatomic stress incontinence (60).

The simple provocative full-bladder stress test is as effective as the radiographic or electronic pressure measurement in detecting urethral incompetence producing stress urinary incontinence (25), but frail elderly patients may not be able to cough, strain, or assume the standing position (61). If provocative full-bladder testing is negative in eliciting incontinence, the other tests should be done (25). The Q-tip test is nonspecific, since many postmenopausal patients without stress incontinence have a positive test (59).

Functional Incontinence. Urinary incontinence can occur in the presence of normal bladder function if the patient is unable to be toileted in an appropriate and timely manner. There is a relationship between urinary incontinence and factors such as poor mobility and confusion (62).

Urinary incontinence among elderly patients in the hospital setting is associated with impaired cognitive and physical functioning (63–65). In nursing home patients, urinary incontinence has been found to be more closely associated with impairments of physical and mental function than with primary bladder problems (17, 66). Since this strong relationship between mobility problems and urinary incontinence exists in elderly patients (67), it is not surprising to find that functional incontinence, secondary to immobility, is a major problem in the nursing home population (68).

Urinary incontinence has been described as "the result of a predisposing factor and a precipitating factor," in which the predisposing factor could be detrusor instability (12). If patients are able to alter their environment and lifestyle to meet the demands of an unstable bladder, they may remain continent (12, 69). The loss of mobility or mental clarity, in addition to the presence of detrusor instability, can result in urinary incontinence (70). Detrusor instability in an elderly patient by itself may not be sufficient to cause incontinence (32, 33), but with additional stress such as dementia or immobility, incontinence may occur (14). The use of anticholinergic medications may not alleviate incontinence in institutionalized patients unless there is also a toileting program to compensate for a patient's limited mobility or cognitive dysfunction (17).

Entities that Defy Classification

Postprostatectomy Incontinence. Continence after radical retropubic prostatectomy is dependent on sphincteric efficiency (71). Preservation of continence following radical retropubic prostatectomy requires a functional urethral length of at least 2.8 cm and a closed, nonobstructed bladder neck (72). Factors such as shortened urethral functional length, decreased urethral closure pressure, and urethral mobility are important in postradical perineal prostatectomy incontinence (73). Approximately 38% of patients report incontinence during the first three months following transurethral resection of the prostate (35). Although in the parkinsonian patient the major risk of incontinence following transurethral prostatectomy is associated with lack of voluntary sphincter control (74), the cause of incontinence after prostatectomy (radical, suprapubic, or transurethral resection) may be bladder dysfunction (detrusor instability or low bladder wall compliance) (75, 76).

The preoperative finding of detrusor instability should alert the physician to the possibility of prolonged postoperative symptoms (28). However, the detrusor response eventually will become normal, and symptoms will disappear in almost all of these patients (28). Although patients who complain of urgency, frequency, and nocturia before prostatectomy are more likely to have detrusor instability, the postprostatectomy symptoms do not correlate well with urodynamic findings (77). Persistent postoperative involuntary detrusor contractions are associated with an unfavorable surgical outcome (78).

Comprehensive urodynamic evaluation is essential before treatment can be recommended for incontinence after prostatectomy (75, 76). Urine flow rate measurement may be used to isolate a group of patients with prostatism symptoms but no bladder outflow obstruction who are unlikely to benefit from surgery (79). A normal flow rate suggests the possibility of nonobstructive bladder disease, such as detrusor instability, whereas a reduced urine flow rate is evidence of bladder outflow obstruction (79).

Although preoperative cystometric findings cannot predict which patients will have involuntary detrusor contractions following prostatectomy (78), it has been recommended that all patients with dementia or a major neurologic disorder be evaluated by urodynamic testing before transurethral prostatectomy (80). Others have suggested that patients with bladder outflow obstruction with a high urgency symptom score (frequency, nocturia, enuresis, urgency) and an unexpectedly high flow rate (greater than 12 mL/sec) need preoperative urodynamic studies (29). Fitzpatrick et al. (77) recommend a urodynamic assessment before prostatectomy for all patients with a combination of frequency, nocturia, and urgency. Kimche et al. (81) recommend that patients with benign prostatic hypertrophy and detrusor instability undergo an examination of the evoked response of the third neural loop in the genitourinary system to ascertain whether there is deterioration of neural function that could cause the instability. Those patients with a low evoked response should not have a prostatectomy (81).

Cerebrovascular Accident. Bladder dysfunction may occur following a cerebrovascular accident (CVA) (82). Although detrusor hyperreflexia, the most common cystometric abnormality in patients with voiding problems following a CVA (83, 84), has been explained by the loss of voluntary control of the reflex arc between the bladder and the sacral spinal cord (14), urinary retention also occurs in patients who have had a CVA. In a study by Borrie et al. (85), 22 poststroke patients with urinary incontinence underwent cystometric studies. The majority had detrusor hyperreflexia, but two patients were reported as being in urinary retention.

Damage to the frontal lobe or internal capsule results in detrusor hyperreflexia (86), which has also been associated with subclinical lesions of the basal ganglia on magnetic resonance imaging (87). The finding of both inhibitory and facilitatory influences by the brain on the sacral micturition reflex arc suggests the complexity involved in predicting bladder dysfunction that may occur in the setting of destructive or irritative neurologic lesions (88). In stroke patients, the contribution to urinary incontinence of cognitive impairment and immobility as well as of neurologic injury needs to be considered (89).

Parkinson's Disease. In Parkinson's disease there is a high incidence of bladder dysfunction (90). Detrusor hyperreflexia has been reported to be the most common urodynamic pattern in patients with Parkinson's disease (91–97). Voluntary control of voiding occurs via the influence of the cortical micturition center on the pontine-mesencephalic reticular formation. The thalamic nuclei, the basal ganglia, and the anterior vermis of the cerebellum also have input into this system (94). In Parkinson's disease, the neurologic lesion in the basal ganglia interferes with voluntary control of the micturition reflex (92). Anticholinergic medications have been reported as useful in the treatment of urinary-incontinent patients with Parkinson's disease (98).

Diabetes Mellitus. In diabetic patients, urinary retention secondary to autonomic neuropathy may be the cause of incontinence (14, 99–101). The loss of bladder sensation, which has been described in diabetics (102–104), results from damage to the afferent nerves from the bladder to the central nervous system (105). This loss of sensation leads to distension of the bladder, decompensation of the detrusor muscle, and urinary retention (106, 107). Treatment is directed at insufficient bladder emptying (108).

Both poor bladder contractility and involuntary bladder contractions have been observed in diabetic patients (109–114). Bradley (115) describes two bladder abnormalities in diabetic patients: detrusor areflexia with impaired sensation, and involuntary contractions of the bladder. The key question is which disorder is responsible for the patient's symptoms. In a diabetic patient with urinary symptoms it seems unlikely that the cause can be accurately determined without further investigation, such as urodynamic studies (114).

Scheduled voiding may be effective for the diabetic patient with a sensory abnormality that results in infrequent voiding; clean intermittent catheterization may be used for the diabetic patient with decreased bladder contractility (116). Careful thought must be given to the decision to suppress involuntary contractions with anticholinergic medications, especially in the diabetic patient who may be prone to urinary retention. Similarly, any medication with anticholinergic activity, such as tricyclic antidepressants, should be used cautiously in diabetic patients (117). The situation may be complicated by a recently described entity in which the bladder contracts involuntarily but is incompletely emptied (118), a condition that also may predispose to anticholinergic-induced retention. Urodynamic studies can be helpful when choosing therapy for the elderly diabetic.

Evaluation of Incontinence

Residual Urine. The residual urine is the urine remaining in the bladder following urination. Measurement of the postvoiding residual urine is a simple way to assess "the effectiveness of bladder emptying" (119). An elevated postvoiding residual urine may indicate bladder outlet obstruction or ineffective detrusor contractions (14). In discussions about urinary incontinence in the elderly, values for a significant volume of residual urine have ranged from 20 mL to 300 mL (13, 14, 120, 121).

It may be difficult to interpret postvoiding residual urine measurements in the evaluation of urinary incontinence, since the normal residual urine in elderly individuals is uncertain. Studies in incontinent women over age 60 have shown that 13% to 29% have residual urine greater than 100 mL (24, 120), and a study of continent women over age 60 reported 13% having residual urines greater than 100 mL (32). In a study of continent men over age 60 (33), only one subject was reported as having residual urine greater than 100 mL.

It is not always possible to predict the type of bladder dysfunction based solely on a measurement of residual urine. In a study of 49 adult men with symptoms of prostatism, Bruskewitz et al. (122) found no correlation between preoperative residual urine volume and the urodynamic findings. Bladder outlet obstruction does not need to be present for a patient to have elevated residual urine. An incomplete bladder contraction that terminates before emptying is complete can elevate postvoiding residual urine (123). Uninhibited contractions may not efficiently empty the bladder (118). Therefore, even without outflow obstruction, urinary retention may occur. On the other hand, there may be unsuspected causes of bladder outlet obstruction. When the periurethral striated muscle relaxes during an uninhibited detrusor contraction, complete emptying can occur.

However, if that muscle contracts during uninhibited contraction, the volume of residual urine will be elevated (124).

There can be problems in obtaining an accurate measurement of the postvoiding residual volume of urine in many elderly patients (125). For one thing, these individuals may not be able to void on command in a testing situation, leading to uncertainty over whether the inability to void spontaneously reflects bladder dysfunction or nervousness. The interpretation of the catheterized urine volume must take this into account. For another, Bruskewitz et al. (122) have noted that measured volumes varied widely in the same individual when postvoiding residual urine determinations were repeated. Although it is suggested that a single measurement may not be definitive, some patients may be reluctant to be catheterized several times.

The measurement of residual urine is an important tool in the evaluation of bladder function. Residual urine volumes less than 100 mL usually indicate normal bladder emptying. High volumes (300 mL or more) indicate problems with bladder emptying. If detrusor instability is found in addition to elevated residual urine, an obstruction of the bladder outlet should be considered. Bladder outflow obstruction can occur in women (126). The residual urine measurement is useful for determining which patients should be referred for further testing.

An accurate residual urine measurement requires that the patient have an adequate opportunity to void prior to catheterization, but because a true measurement of the postvoiding residual urine in an elderly patient may be difficult, the residual urine measurement is most useful when considered along with all other available data.

Urodynamic Studies. Urodynamic studies can be useful in the evaluation and treatment of incontinence in the elderly (21, 127), but they are not without cost and risk (128), and some controversy exists concerning using urodynamic studies to evaluate incontinent elderly patients (129). A technologically simpler approach to evaluation may be desirable (120). If the cause of incontinence could be determined by history and noninvasive examination, then urodynamic studies could possibly be avoided (100). Simple cystometry can be helpful to assess bladder function among incontinent geriatric patients in settings in which formal urodynamics are either unavailable or impractical (130).

Since there is a poor correlation between the symptoms of urinary incontinence and urodynamic abnormalities, patients may require further investigation to determine the cause of the problem and to decide on the treatment (21, 131). A medical history and physical examination are helpful in predicting urethral incompetence in patients with simple, clear-cut symptoms of exertional or stress incontinence (25). When the symptoms are urge, mixed stress and urge, or suggestive of overflow incontinence, cystometry, residual urine measurement, and provocative full-bladder stress testing are needed (25). Single-channel cystometry, when used in conjunction with simple urethral tests, can provide most of the information that is obtained with multichannel cystometry, in which abdominal pressure is electronically subtracted from total bladder pressure (132), and visual confirmation of urine leakage with coughing is useful (132). Complex urodynamic tests should be reserved for complex symptomatology (25).

Some cases of detrusor instability diagnosed by cystometry may be false positives. Detrusor instability can be provoked by the use of a gas at a rapid filling rate (34), and the clinical relevance of this requires further investigation. Day-to-day variability in cystometric findings has been reported in elderly patients (61).

Cystometric improvements are not synonymous with clinical benefit (133).

Cystometry: Bladder Sensation. The measurement of volume at first sensation that is obtained during cystometry can be difficult to interpret unless it is markedly elevated. The "normal" volume for sensing bladder filling is not clear. In a group of normal adults ranging in age from 16 to 85 years, Merrill et al. (134) described the volume at first sensation as ranging widely from 30 mL to 460 mL (mean, 137 mL). Andersen et al. (33) studied a group of healthy elderly men and found the bladder volume at first sensation to range from 20 mL to 200 mL (mean, 127 mL). It has been pointed out that because sensation is subjective, it is not easy to evaluate (135). The patient's ability to sense bladder filling is difficult to assess, although it is an important component of bladder function.

Urinary Flow Rate. In men, the peak urinary flow rate decreases with increasing age (136), but for normal women, it does not deteriorate much (137); the decrease in men is an average of 2 mL/sec per decade, whereas in women it is only 0.3 mL/sec per decade (137). Although most men with bladder outlet obstruction have a diminished flow rate, uroflowmetry as a single examination cannot distinguish between bladder outlet obstruction and impaired detrusor contractility (138).

Urethral Pressure Profile. The role of the urethral pressure profile in the evaluation of elderly incontinent patients is uncertain (15).

Management

Diapers. Although treatment can be directed at the specific cause in an attempt to eradicate incontinence, in recent years the use of absorptive pads has increased (12, 139). The disposable diaper, which has become popular in the care of the incontinent patient, has advantages and disadvantages.

The adult diaper is used frequently for incontinent nursing home patients (10). Although the diaper simplifies the nursing care of the incontinent patient (140, 141) and allows increased mobility and socialization by the patient (142), it does not cure incontinence (143). The diaper may be difficult to remove for the elderly patient who wishes to void at the toilet. In addition, the diaper may indicate to both the staff and the patient that incontinence is medically acceptable. Some individuals experience a loss of dignity when wearing a diaper because it is associated with infancy (12, 142). The cost of using a disposable product for the long-term must also be considered (142, 144).

Toileting requires more staff time than does the changing of a diaper (145), and skin irritation and breakdown may develop if diapers are not changed at appropriate intervals (12). Before diapers are used, an attempt should be made to determine the cause of incontinence and to use that information to choose an effective treatment. Permanent use of diapers should be a treatment of last resort (14). In cases where specific treatment fails, diapers may be the only alternative (12).

Stress Incontinence. Surgery is an effective treatment of pure stress incontinence associated with urethrocele (146). The goal of most operations is to elevate the bladder neck to within the abdominal zone of pressure (147). Urethral sling procedures pass a ribbon of fascia or artificial material beneath the urethra, which elevates and compresses it (146). Although norephedrine, an alpha-adrenoreceptor stimulating agent, produces a significant increase in maximum urethral closure pressure, the therapeutic effect is moderate (148). Oral estriol and phenylpropanolamine in combination have been recommended for the treatment of stress urinary incontinence in postmenopausal women (149).

Pelvic Floor Muscle Exercise. Pelvic muscle exercise (perivaginal muscle contraction and relaxation) is advocated to prevent and treat stress urinary incontinence, for it is thought to increase urethral resistance by increasing periurethral muscle tension (150). It has been recommended that exercises (a 10-sec pubococcygeal contraction followed by a 10-sec relaxation) be done at least 80 times per day (58). This therapy may not be applicable to most elderly patients.

Behavioral Treatment. Behavioral treatment requires that patients be able to learn new skills and participate actively in their own treatment for several weeks (151). Behavioral training with biofeedback should be considered among the first treatments offered to nondemented patients with stress or urge incontinence (152, 153). Biofeedback enables suitably motivated patients to learn voluntary control by observing the results of attempts to control bladder, sphincter, and abdominal pressure responses (152). For stress incontinence, the primary goal of training is to enable the patient to contract the periurethral muscles selectively while inhibiting contraction of abdominal muscles; for urge incontinence, the goals are to train the patient to inhibit detrusor contraction voluntarily and to contract periurethral muscles selectively to prevent urine loss until detrusor inhibition can be achieved (152).

Scheduling regimens used as behavioral interventions for urinary incontinence include bladder training, habit retraining, timed voiding, and prompted voiding (154). In bladder training, the patient progressively extends the intervoiding interval; in habit retraining, the toileting schedule is adjusted to fit the patient's individual voiding pattern (episodes of incontinence, patient's desires to void); in timed voiding, the patient is given a fixed voiding schedule that remains unchanged; with prompted voiding, the patient is asked at regular intervals if she needs to void and is assisted in using the toilet only if the response is positive (154).

Urinary incontinence in elderly, nondemented, ambulatory, community-dwelling patients can be effectively treated by a nurse practitioner and internist/geriatrician utilizing behavioral training with or without bladder-sphincter biofeedback (155). Bladder training is beneficial in noninstitutionalized older women with stress incontinence alone, those with detrusor instability alone, and those with both detrusor instability and stress incontinence (156). However, bladder retraining programs in the nursing home setting may require an impractical amount of nursing care (157).

Detrusor Instability. In some cases, involuntary contractions of the bladder may be treated with bladder retraining or anticholinergic medications. Urinary tract infection should be treated with antibiotics. Patients with involuntary bladder contractions may require additional urologic evaluation to determine the cause of the dysfunction—inflammation, neoplasm, prostatic hypertrophy.

Drug therapy plays a minor role in the treatment of detrusor instability (158). Anticholinergic medications have been utilized in the treatment of detrusor instability. Oxybutynin chloride has both an anticholinergic effect and a direct spasmolytic effect on the bladder smooth muscle (159). Oxybutynin chloride at dosages of 2.5–5 mg, three times per day, is safe for use in the elderly; dryness of the mouth is the most common side effect (160). There have been a limited number of clinical trials of oxybutynin in incontinent elderly patients. Neither a habit-training program alone nor one combined with oxybutynin was shown to have any significant effects on the frequency of incontinence in a placebo-controlled trial involving functionally impaired nursing home patients with detrusor hyperreflexia (161). In a study of elderly institutionalized patients with detrusor instability, oxybutynin was no more effective than placebo for the treatment of incontinence (162). In an uncontrolled study of the effects of oxybutynin in eight adult patients with involuntary contractions of the detrusor, Diokno and Lapides (163) demonstrated symptomatic improvement in all patients and urodynamic improvement in seven of the eight. Moisey et al. (159) conducted a controlled study of 23 patients with detrusor instability (age range, 20–79 years) in which patients received 28-day courses of placebo or oxybutynin chloride (5 mg three times a day). Although 17 patients (69%) had symptomatic improvement, urodynamic changes did not match the symptomatic improvement in most of them. Oxybutynin chloride administered intravesically has been suggested for the management of patients who do not respond to oral mediations or who have intolerable side effects (164).

Although imipramine has a place in the treatment of urinary incontinence associated with detrusor instability in the elderly (133), elderly incontinent patients do not do significantly better with imipramine and bladder training than with bladder training alone (158). Elderly patients with urinary incontinence and detrusor instability who are treated with bladder training and imipramine do well if they have good cognitive function and good mobility (165). Patients are easier to cure if detrusor instability is less severe—that is, the involuntary contraction occurs at a higher volume, reaches a lower pressure, or is sustained for a shorter period (165).

Pinacidil, which inhibits contractile activity in smooth muscle by the opening of potassium channels, has not been effective for the treatment of unstable detrusor contractions associated with bladder outflow obstruction (166).

The aim of regular toileting is to prevent incontinence by emptying the bladder before the contents reach the volume at which an involuntary contraction occurs (167). Toileting may fail in patients with small bladder capacities (involuntary contractions occurring at volumes less than 150 mL) because toileting more frequently than every two hours is difficult (167). Even if incontinence occurs, toileting must be done regularly because some urine may remain in the bladder if the involuntary contraction is not sustained (167).

Nursing Homes. Nonurological problems (behavioral problems, cognitive dysfunction, immobility, medication problems, diabetes, local pathology), which frequently contribute to urinary incontinence in long-term care facilities (17, 61, 66, 168), should be addressed prior to considering urodynamic studies (168). The frequency of incontinence was reduced in nursing homes with a behavioral approach whereby patients were "prompted" hourly and toileted only when they asked for assistance (169–171). Some of the improvement may have occurred because the patients learned to request help (171). Patients with normal bladder capacity and patients who were more cognitively intact responded better to the behavior therapy program (171). Electrical stimulation with a rectal probe is not effective by itself in improving urinary incontinence in functionally impaired nursing home patients (157).

Unfortunately, a regular toileting schedule may be difficult for the nursing staff to maintain (145), and toileting programs are more likely to be successful with either an increase in trained personnel or a more productive redistribution of the work (172). The systematic toileting of patients may improve the quality of patients' lives, although the nursing home may not experience a savings in labor and supply cost (173).

Summary

The training of health care providers in the diagnosis and management of urinary incontinence is inadequate, and evaluation and management skills are less than optimal (22). Urinary incontinence volume measurement is difficult to perform accurately in elderly long-term-care inpatients (174). After incontinence has been noted, the physician needs to select the appropriate studies to determine the cause and choose the correct treatment. Otherwise, treatable causes such as outlet obstruction or fecal impaction may be missed. Subsequent management includes scheduled visits to the toilet, treatment of impaired mobility, use of easily identified and accessible toilet facilities, reevaluation of the need for restraints and side rails, and, if appropriate, the use of drugs to treat the incontinence. Many elderly incontinent patients who are treated in the outpatient setting can be cured or substantially improved (15).

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Falls in Older Persons

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Falls are a common problem for older persons. Studies indicate that up to one-third of community-dwelling persons over age 65 fall annually (1, 2), and approximately one-half of these have more than one fall (1). The prevalance of falls is equally problematic among older persons in institutional settings. Falls in the acute-care hospital are a leading cause of adverse effects, and older patients experience the overwhelming majority of falls (3), as many as 10% of these older hospital patients falling repeatedly (4). About 50% of nursing home residents fall every year (5), and up to 40% have recurrent falls (5). The risk of falling increases with age. The fall rate (number of falls per 100 person-years) increases from 47 for those aged 70–74 to 121 for those aged 80 and older (2). The fall rate is equal for men and women (2).

Within the next few decades the older population—especially those persons aged 75 and older, who are at greatest risk of falling—will increase, and physicians in all specialties will be faced with and challenged by the problem of falls in older people. The purpose of this article is to review the consequences of falls, the conditions under which falls occur, the factors associated with risk of falling, and intervention strategies designed to reduce that risk.

Consequences of Falls

Falls are associated with significant morbidity and mortality. Falls are a leading cause of mortality due to "accidents" or unintentional injury, with up to 9,500 deaths per year attributed to falling (6). For those surviving a fall, significant morbidity is likely to follow. About 5% of falls of all older persons, whether living in their community or institutionalized, result in a fracture (1). Hip fractures are the most serious. After repair of a hip fracture, many persons never regain their previous level of ambulation. Approximately 60% of persons experience decreased mobility, and another 25% become functionally dependent in ambulation and require either mechanical (cane, walker) or human assistance in walking (7). Women have a higher rate of hip fracture than men, partly owing to low bone mass (8). Osteoporosis can either result in spontaneous hip fractures or lead to fractures that occur from the impact of a fall onto hard, nonabsorbing ground surfaces. An additional 10% of falls result in nonfracture injury (1), including hematomas, joint dislocations, muscle sprains, and head injuries.

In the absence of physical injury, falls are by no means innocuous. Up to 50% of those who have had a fall admit to avoiding activities, typically those that led to the fall, because of a fear of further falls or injury (9). The risk of developing a fear of falling is increased in those persons who have underlying gait and balance disorders and who have recurrent falls over a short period; the risk is greatest in those who suffer injury, functional decline, or prolonged postfall lie times—inability to get up from the floor by oneself. Any immobility that occurs as a result of injury or fear of falling places persons at risk for a host of complications, including deep venous thrombosis and pulmonary embolism; sepsis arising from decubitus ulcers, urinary tract infections, and hypostatic pneumonias; muscle atrophy; and joint contractures. The likelihood of incurring a complication is in direct proportion to the duration of immobility.

Falls experienced by older persons are also

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distressing for family members. At issue is whether the person can live at home alone and remain safe or requires protective nursing home placement. Falls and instability are a contributing factor in up to 40% of nursing home admissions (6).

Causes of Falling

Falls are likely to occur during any activity that results in balance displacement (walking, climbing and descending stairs, transferring onto or off chair or bed) and in which the body mechanisms responsible for controlling stability fail. In older persons, the catalysts for balance loss and subsequent falls are intrinsic factors, such as age-related physiologic changes, pathologic conditions, and medication effects, and extrinsic factors or environmental hazards.

Among the elderly, the causative factors for falls vary widely. For fit and active persons, a fall may be "accidental," the consequence of adjusting to age-related changes (such as a decline in visual function) in interaction with unfavorable environmental conditions (such as the presence of an uneven ground surface). Failure to recognize a curb edge or door sill in one's path can lead to tripping and the risk of falling. However, the onset of falling is more serious for frail persons in poor health. For these individuals, falls are typically a sign or symptom of underlying pathologic conditions, adverse drug effects, and unsafe environmental conditions, factors that may be present either separately or in combination to precipitate a fall.

Age-Related Physiologic Factors

A number of physiologic changes occur with age and contribute to postural stability and fall risk. The most important changes occur in the visual and neuromuscular systems, affecting gait and balance and altering a person's ability to maneuver about the environment safely.

Vision. Visual function, the ability of the eyes to adjust to various environmental stimuli, diminishes with age. Because the response to varying levels of light and darkness is reduced (10), persons require more time to adapt to changes in lighting, for example in moving from areas of bright illumination to areas of darkness. Dark adaption, the capability of the eye to adjust to low levels of illumination, is particularly affected by age and is associated with the risk of falling (11). This change compromises the ability to recognize potential environmental hazards under conditions of low illumination. Bright lighting produces similar effects. With age, pupillary response and accommodation declines (10), and consequently, excessive illumination may lead to momentary blindness until the eyes adjust to it.

A greater sensitivity of the aging eye to glare—a dazzling effect associated with a source of intense illumination—can interfere with vision and increase fall risk. Common sources of glare include sunlight and unshielded or exposed light bulbs. These sources can also result in reflected glare off polished floor surfaces, thus hiding from view potential ground hazards that can lead to slips and trips. Glare on floor surfaces is perceived by older persons as slipperiness. To compensate, they may alter their gait, assuming a pattern that is slower and flat-footed, with a wide base of support. However, such adaptions may not be possible for persons with neuromuscular abnormalities and, when attempted, may lead to instability and falls.

Depth perception also declines with age (10). As a result, environmental objects of low visual contrast and thus indistinguishable from their background, such as carpet and step edges and door sills, may not be easily visualized. Patterned, checkered, or floral floor tiles and carpet designs may appear to the aging eye as having either ground elevations or depressions, possibly leading to hazardous gaits.

Balance and Gait. Maintaining balance is dependent on correct functioning of the sensory and motor or musculoskeletal systems. Within the sensory system, proprioception, vestibular input, and vision are the most critical. Operating in unison, these components culminate in postural sway, an anteroposterior and lateral motion of the body that counters the effects of gravity and controls stability. Proprioceptive feedback, arising from muscle, tendon, and joint receptors in the limbs and neck, provides the body with kinesthetic information and orientation with respect to environmental conditions. The vestibular system detects linear and angular displacements of the head (via receptors located in the semicircular canals and otolith organs) and, in response to displacements of balance, initiates a righting reflex that consists of a series of compensatory limb, trunk, and head movements that control stability. The visual system provides the majority of the sensory input needed for gait and balance. Visual input helps one to perceive cues within the surrounding environment—to detect altered linear and angular motions of the visual field—and supplies the body with information on its orientation in space. In addition, vision facilitates proprioceptive and vestibular feedback, and, in the event of any deficiencies, vision serves as a substitute to preserve balance.

The musculoskeletal system provides postural support (proper body alignment), muscular strength, and joint flexibility to maintain balance and correct body displacements. When standing, a person maintains balance by constantly positioning the body's center of gravity (COG) over a base of support (BOS), the area surrounding the feet, by utilizing an ankle strategy that consists of rotating the body about the ankle joints. During ambulation, the COG extends beyond the BOS and stretches the limits of stability. This displacement is detected by the sensory systems, which, in turn, send a group of messages to stretch receptors in the joints and muscles of the lower extremities. To regain stability through realignment of the COG over the BOS, a series of postural maneuvers are initiated. Depending on the size of the displacement, either a hip strategy consisting of flexing or extending the hips or a stepping or stumbling strategy consisting of a rapid forward or backward shifting movement of the feet is employed, in conjunction with a righting reflex or response.

Also, gait—the manner of walking—is predominantly a function of the musculoskeletal system. The gait cycle consists of a stance and a swing phase. Ambulation is brought about by a series of alternating leg movements: pushing off on the leg in stance while, at the same time, swinging the other leg forward. To allow for adequate ground clearance during the swing phase, the knee becomes flexed and the ankle dorsiflexed. When the heel of the swing leg strikes the ground, a return to stance, the knee becomes extended and the foot plantar-flexed to provide body support.

Any disruption in the effective coordination of sensory and musculoskeletal movements jeopardizes postural stability and gait and increases the likelihood of falls. With age, proprioceptive feedback declines, and its malfunction is associated with increased postural sway to a level of unsteadiness (12). Vision can compensate for proprioceptive loss and support balance, as demonstrated by older persons with proprioceptive loss who ambulate by visually observing the ground to ensure correct foot placement. However, when visual input is decreased, maintaining balance becomes difficult, as evidenced when a person is asked to stand with eyes closed or to walk in a dark room; sway increases and balance becomes unsteady. Also, a decline in visual perception may alter the processing of visual information and predispose to instability. Older persons who fall have more difficulty than nonfallers in estimating true horizontal and vertical planes in their visual fields (13). In addition, dependence on visual input for balance is often inadequate because visual feedback to control stability is often slow, and any correction for change is delayed in older persons (14).

The vestibular righting response also diminishes with age (15). As a result, if a person trips or slips—experiences a displacement of balance—the chances of recovering stability decline. Within the musculoskeletal system, posture becomes more kyphotic, related, in part, to osteoporosis and muscular weakness (16), possibly altering an individual's balance threshold because the COG is shifted forward, extending beyond the BOS. In addition, muscular strength in the legs and ankles declines, and joint flexibility becomes impaired with age (17), impairing the effective application of ankle, hip, and stepping strategies to correct balance.

Changes in musculoskeletal function contribute to a number of gait alterations. Compared to younger persons, the gait of older persons is decreased in speed, stride length (the distance the foot travels during the swing phase), heel lift (the level of ground clearance by the foot during the swing phase), and the ability of the foot to fully plantarflex and dorsiflex (18). As a consequence, gait becomes less steady, and the execution of motor strategies to adjust balance displacements is impaired.

Although older persons normally are slow in detecting and responding to postural disturbances, there is a good deal of reserve and redundancy in the sensory information and motor function needed to maintain gait and balance. Failure of one source of input can be compensated for by feedback from another system; for example, visual input can compensate for a decline in proprioceptive feedback. Similarly, when perturbed, older persons with impairments are able to resort to alternative motor strategies. If ankle strategies cannot be employed because of lower-extremity weakness, older persons are able to compensate by using a hip strategy—a proximal-to-distal sequence of thigh and trunk muscle contractions—to preserve balance. However, dysfunction in more than one system is likely to result in a lowered balance threshold and increased fall risk.

Pathologic Conditions

Acute and chronic medical problems that affect gait and balance are more decisive in causing falls than age-related physiologic changes not accompanied by medical problems. It has repeatedly been demonstrated that fallers tend to have more medical diagnoses than nonfallers (1). The responsible acute diseases include any condition that interferes with postural stability, such as syncope, hypovolemia, cardiac arrhythmias, electrolyte disturbances, stroke, and sepsis (urinary tract infections, gallbladder disease, pneumonias).

Chronic diseases that may exacerbate postural instability and lead to gait impairments originate in the visual and neuromuscular systems. For example, diseases of the eye, such as cataracts, macular degeneration, and glaucoma, significantly interfere with visual function and are strongly associated with both the risk of falls and hip fractures (9, 19). Impaired vision becomes an even greater risk factor when combined with poor environmental lighting conditions.

Parkinson's disease is associated with a loss of the postural reflexes of propulsion (uncontrolled forward motion of the body) and retropulsion (producing loss of balance backward). Persons with Parkinson's disease also exhibit a number of gait changes: walking becomes short-stepped and shuffling, barely clearing the floor; persons typically display poor initiation and hesitancy or freezing of gait. Lower extremity hemiplegia or paresis results in a diminished BOS and decreased ankle dorsiflexion on foot clearance when walking.

Arthritis of the hips and knees can lead to decreased single limb support (the result of pain when bearing weight), altered gait (reduced stride length, ground clearance), and instability (unstable and inflexible joints resulting in poor corrective responses). Neuropathy, osteomalacia, thyroid disease, and deconditioning can lead to lower extremity muscle weakness, contributing to altered gait and balance; for example, gluteal muscle weakness results in exaggerated trunk movements and waddling gait. Foot abnormalities such as bunions, hammertoes, or heel spurs can lead to mechanical gait impairments.

Alzheimer's disease is associated with poor gait (reduced proprioception and steppage height), altered visual input (visual spatial and field defects), and impaired judgment (inability to distinguish between safe and unsafe activities and environmental conditions).

Medications

Certain medications are known to interfere with postural stability and gait and to increase fall liability. The most common include sedatives, antipsychotics, antihypertensives, and antidepressants (6, 9). These can lead to increased sedation, delayed reaction times, orthostasis, movement disorders, and cognitive impairment such as diminished awareness of hazards. The risk of drug-related falls increases with long-acting medications and polypharmacy (taking more than four drugs simultaneously) (1).

Extrinsic Factors

The overwhelming majority of falls, whether in the community or in institutional settings, take place in the bedroom and bathroom (20). This may reflect the increased time older persons spend in these locations or, more important, may represent difficulties in the performance of mobility tasks. Several environmental obstacles and design features are associated with falling: too low or too high beds and elevated side rails; low chair seats and poor armrest support; low-seated toilets and poor grab-bar support; poorly illuminated areas; elevated ground conditions (door thresholds, thick pile carpeting); and slippery ground surfaces (wet or polished floors, non-slip-resistant bathtub surfaces, sliding rugs) (20). The type of footwear, including fit, thickness and slip resistance of soles, heel height, and the condition and proper utilization of assistive devices (canes, walkers) also influence gait and balance. The likelihood of environmental conditions contributing to falls is greatest in those persons with altered mobility. Often, the presence of environmental obstacles exceeds the person's functional ability to walk and transfer safely and interferes with their ability to compensate.

Interventions

The goals of fall prevention are to maximize mobility, reduce the threat of injury, and maintain autonomy. Interventions designed to accomplish these goals encompass medical, rehabilitative, and environmental approaches.

Medical Interventions. The medical approach is twofold: first, to identify persons at risk of falls and, for those with a history of recent falls, to uncover the causative factors; second, to attempt to modify any discovered risk factors.

The identification of fall risk is determined by reviewing the person's medical history for contributory conditions and medications, including a history of recent falls, lower extremity dysfunction, arthritis of the hips and knees, gait and balance impairment, altered cognition, visual disorders, postural hypotension, bladder dysfunction (nocturia, incontinence), and use of certain medications (psychotropics, sedatives, hypnotics, antihypertensives) (5, 6).

In the absence of historical risk factors, altered mobility is a strong indicator of fall risk (21). Mobility dysfunction is ascertained by asking the person to perform a number of gait and balance maneuvers. The person should be observed sitting and rising from a chair, standing with eyes closed (the Romberg test to assess proprioceptive function), maintaining postural stability when perturbed (this is a sternal push test accomplished by lightly pushing on the sternum and initiating displacement), and walking in a straight line and turning around. An inability to perform one or more of these maneuvers indicates a risk of falling. Moreover, an abnormal finding signifies the presence of an underlying intrinsic or extrinsic problem (**Table 1**). The presence of historical risk factors or mobility dysfunction should trigger further investigations aimed at modifying the responsible factors.

TABLE 1
Differential Diagnoses of Mobility Dysfunction

Impaired maneuver	Causes	
	Intrinsic	Extrinsic
Chair transfer	Parkinsonism Arthritis Deconditioning	Poor chair design
Standing balance	Postural hypotension Vestibular dysfunction Adverse drug effects	
Romberg test	Proprioceptive dysfunction Adverse drug effects	Poor illumination Overly absorptive footwear or carpeting
Sternal nudge test	Parkinsonism Normal-pressure hydrocephalus Adverse drug effects	
Walking, turning	Gait disorders (parkinsonism, hemiparesis, foot problem) Sensory dysfunction Adverse drug effects	Improper footwear Improper size or use of ambulation devices Hazardous (slippery, uneven) ground surfaces

In those persons who have had falls, the evaluation begins with a history of the surrounding circumstances of the event(s). Inquiries need to be made about symptoms experienced, location of the fall, activity performed at the time, and time or hour of the episode(s). This information provides important clues to causative factors. For example, an individual who has had one or more falls who complains of dizziness and falls during transfers in or out of bed or rising from a chair may have orthostatic hypotension.

Once the history of falls is obtained, past medical problems, current complaints, and medications should be reviewed. A physical examination and diagnostic studies should follow, the extent of both determined by the historical information gathered and clinical suspicions. The goal of the medical evaluation is to rule out contributing acute and chronic disease processes and medications and to treat each accordingly.

Rehabilitative Interventions. Those persons who fail to improve with medical treatment and continue to remain at risk of falling may respond to a number of rehabilitative strategies. For those with chronic neuromuscular disorders, a focused program of exercises aimed at correcting gait and balance impairments may be beneficial in reducing risk (22). For example, in persons with degenerative arthritis, stretching exercises directed toward enhancing joint flexibility and strengthening the hip and knee extensor and flexor muscles can improve mobility. For persons with Parkinson's disease, ambulation training, proximal and ankle muscle strengthening, and postural exercises can enhance both gait and balance. For those with dementia, a daily program of walking can offset altered gait and balance that commonly results from immobility, and participation in a regular program of exercise has been shown to improve cognitive functioning and may reduce falls that result from poor judgment, such as taking part in hazardous activities (22). In older women with osteoporosis, weight-bearing exercises can minimize further bone loss, thereby reducing the risk of fracture. For those whose bone density is already well below the fracture threshold, exercise may be useful for its effect on proximal muscle strength and coordination of gait and balance, ultimately reducing fall risk.

Attention to footwear can support safe patterns of gait. Shoes with rubber or crepe soles provide adequate slip resistance on most ground surfaces. Socks with nonskid treads are helpful for persons who prefer to walk about barefooted. High-heeled footwear should be avoided because it decreases the standing and walking base of support and promotes loss of balance; shoe heels no more than 3.5 cm in height and at least 5.5 cm in surface width provide maximum balance support.

An ambulation device (cane, walker) for per-

TABLE 2
Environmental Hazards for the Elderly and Corrective Modifications

Hazard	Modification
Illumination	
Low lighting	Install good lighting in all living areas, with switches at room entrances; night lights along route from bedroom to bathroom; lamp next to bed; stairways and steps especially well lighted
Glare	Control window glare from sunlight with Mylar or translucent shades; they eliminate glare but do not reduce existing illumination Eliminate glare from exposed light bulbs by using translucent light shields Eliminate floor glare from lights shining directly on polished floor surfaces by using carpeting or redirecting light sources
Ground Surfaces	
Slippery area rugs	Place slip-resistant matting underneath rugs to firmly anchor them
Upended carpet edges	Tack or tape down (with double-sided adhesive tape) carpet edges
Slippery tiled or linoleum kitchen and bathroom floor surfaces	Apply nonskid adhesive floor strips near areas that are likely to become wet (sink, toilet)
Raised door sills	Place carpeting over raised sills to create a smooth transition surface between rooms
Furnishings	
Furniture obstructs pathways	Rearrange furniture not to protrude into natural walkways
Low seats on chairs	Supply chairs with armrests to provide leverage and compensate for low seat height; add a cushion to raise seat height
Too low or too high bed height	Replace existing mattress with one either thinner or thicker to lower or raise bed height
Shelves	
Kitchen and closet shelves too low or too high for safe reach	Use either sturdy stools with handrails or hand-held grabber device, or place items on reachable shelves (between person's eye and hip level)
Stairways	
Stairs lack handrails	Install well-anchored cylindrical handrails (for hand grasp)
Inadequate stairway lighting	Provide accessible day and night lighting with switches at top and bottom of stair
Stairway steps not contrasting	Apply color-contrasted adhesive tape to step edges
Slippery stairway steps	Apply nonskid treads to all steps
Bathroom	
Slippery bathtub floor	Apply nonskid strips or install rubber mat; provide bath seat and extended shower hose
Slippery bathtub rim	Install portable grab bar to side of tub
Slippery sink tops and towel bars	Apply nonskid adhesive tape to sink tops (for hand grasp) and replace towel bars with grab bars
Low toilet seats	Use elevated toilet seats; install grab bars on toilet seat or wall

sons with underlying gait or balance disorders improves mobility by increasing the person's standing and walking base of support, providing additional points of ground contact, and improves stability by supplying proprioceptive feedback through the handle. Such a device also provides a sense of confidence and helps reduce the fear of instability and falls. To ensure optimum function, ambulation devices need to be "prescribed"—designed for specific gait and balance problems and tailored to fit the person and his or her environmental setting.

Environmental Interventions. Environmental interventions aimed at reduction of falls consist of identifying and eliminating hazardous conditions that interfere with mobility. The best method of determining whether a particular environmental area or furnishing is safe or hazardous is to observe the person's mobility. Ask the person to walk through every room and over floor surfaces, including rugs, carpets, and tiled surfaces, to transfer on and off beds, chairs, and toilets and in and out of bathtubs, to climb and descend stairs, and to reach up and bend down to obtain objects from kitchen and closet shelves. Those environmental features that interfere with mobility can be altered (**Table 2**).

Summary

Falls are a common problem for older persons and result in significant mortality and morbidity. Most are caused by multiple intrinsic and extrinsic factors that have cumulative effects on mobility. Preventive interventions are aimed, first, at identifying and assessing fall risk and, second, at attempting to reduce those risks.

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Falls Prevention:

The Efficacy of a Bed Alarm System in an Acute-Care Setting

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Abstract

The present study examined the clinical efficacy of a bed alarm system in reducing falls from bed on a geriatric evaluation and treatment unit. A nine-month case-controlled study was designed, in which 70 patients (60 women, 10 men; mean age 84 years, range 67–97 years) at increased risk for bed falls were randomly assigned to either an experimental or a control group. Subjects in the experimental group ($n = 35$) received a bed alarm system and those in the control group ($n = 35$) did not. Outcome measures included bed falls, performance of the bed alarm system, and staff attitudes toward the use of the system. Although results failed to demonstrate a statistical difference in bed falls between the experimental ($n = 1$) and control ($n = 4$) groups ($p = 1.00$), there was a clinical trend toward reduced falls in the experimental group. The system functioned properly, activating an alarm in all instances when patients were transferring from bed, and with the exception of one case, nurses could respond in a timely fashion to assist patients and prevent bed falls. The system did not produce any adverse effects in patients, nor did the device interfere with the rendering of medical care. The system was well accepted by patients, families, and nurses. These data suggest that bed alarm systems are beneficial in guarding against bed falls and are an acceptable method of preventing falls.

Patient falls are a leading cause of adverse events in acute-care hospitals, accounting for up to 40% of all incidence reports (1). The majority of falls occur in patients 65 years of age and older (2). Up to 75% take place during transfers out of bed (3) and occur most frequently in patients with diminished mobility and cognitive skills. Bed falls in older patients are associated with a number of morbid complications, including soft tissue injury, fractures, and immobility due to a fear of further falls. Mechanical restraints are often employed to prevent falls; the prevalence of mechanical restraints on general medical floors ranges from 7% to 17% (4). Despite the use of such restraints, patients continue to experience bed falls (5). As a result, bed alarm systems (BAS) have been enlisted as alternative fall prevention measures.

Such devices warn nursing staff that patients who should not be leaving their beds unassisted are doing so. The bed alarm systems function by allowing patients to maintain a free-movement zone or area for normal activity in bed, including turning around or rolling over. When patients leave their beds and thus exceed the free-movement zone, an alarm sounds, indicating that the patient is about to transfer unsafely from bed. While the use of these alarm systems to guard against bed falls appears attractive, little research on their performance and acceptance has been published, aside from scant anecdotal reports attesting to their benefits (6, 7). Therefore, a case-control prospective study was undertaken to determine the efficacy of one such system to reduce the number of bed falls in an acute-care hospital setting.

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Methods

The study was conducted in the Geriatric Evaluation and Treatment Unit of The Mount Sinai Medical Center, New York City. The unit is a 16-bed acute-care facility designed specifically to provide multidisciplinary medical care to older patients. All patients admitted to the unit between January 1 and September 30, 1992, were evaluated by performance-oriented environmental mobility screen, an observational tool used to assess bed mobility and the risk of falling (**Fig. 1**). Patients are observed performing a number of transfer maneuvers and are scored as either normal or abnormal on each. One or more abnormal scores signifies poor bed mobility and increased fall risk.

Patients demonstrating poor bed mobility were randomly assigned to either the experimental group that received an alarm system or the control group that did not receive one. Informed consent was obtained from all patients in the experimental group and their family members prior to their being given an alarm. The unit staff were not blinded to the intervention. Both groups were given equal nursing attention to prevent falls: hourly visual checks, mechanical restraints as clinically indicated. The number of falls, the surrounding circumstances of each, and any resultant physical injury were recorded for both groups during the course of their hospital stay. "Falls" were defined as all events for which staff filed an incident report indicating a fall. The difference in number of falls from bed occurring in the experimental and the control group served as an outcome measure to evaluate the efficacy of the system. Fisher's exact test was used to determine the statistical significance of the difference.

The system used in this study was the RN+ OnCall bed monitoring system (**Fig. 2**), consisting of a pressure-sensitive pad placed on top of the patient's mattress and underneath the bed sheet. In bed, the patient rests on the pressure pad. If the patient sits up, the pressure on the sensor pad is relieved, activating both an audio and a visual alarm to a separate console located at the nursing station.

Additional data collection for the experimental and control groups included diagnoses and medications taken on admission and the use of mechanical (physical) restraints and bed rails during the patient's hospital stay. Data on system performance included number of patient-use hours; number of alarm activations; reasons for alarm activation (why the patient was transferring out of bed); number of true alarms (patient was actually exiting the bed) and patient's location (for example, sitting in bed, climbing over side rails, or out of bed and walking about); number of false alarms (for instance, patient lying supine in bed awake or asleep, but not getting out of bed); average nurse response time per alarm activation; presence of adverse affects (system interfered with treatment or caused the patient harm); and attitudes of patients, family members, and nursing staff toward the system. This information was collected and recorded by the nursing staff on each shift.

OBSERVATION

NORMAL	ABNORMAL
▪ Bed transfer is smooth, controlled movement (sits on and rises from bed in one attempt)	▪ Bed transfer is not smooth (requires several attempts to sit or rise; falls on to mattress; uses mattress edge to guide transfers)
▪ Sitting balance is stable	▪ Sitting balance is unstable
▪ Does not use arm support to maintain sitting balance	▪ Uses arm support to maintain sitting balance
▪ When seated both feet rest flat on ground	▪ Feet do not rest flat on ground
▪ Able to lie down (in supine position) and rise in one smooth controlled movement	▪ Unable to lie down (in supine position) and rise in one smooth, controlled movement
▪ When seated feet do not slide away on ground	▪ Feet slide away
▪ Able to operate nurse call system	▪ Unable to operate nurse call system
▪ When seated bed does not slide away	▪ Bed slides away
	▪ Unable to perform unassisted bed transfers

Fig. 1. Performance-oriented environmental mobility screen.

Results

The experimental and the control group each consisted of 35 patients (30 women; 5 men), mean age 84 years and range between 67 and 97 years. Patients had one or more acute medical problems or underlying chronic neuromuscular conditions (altered cognition, gait and balance disorders)

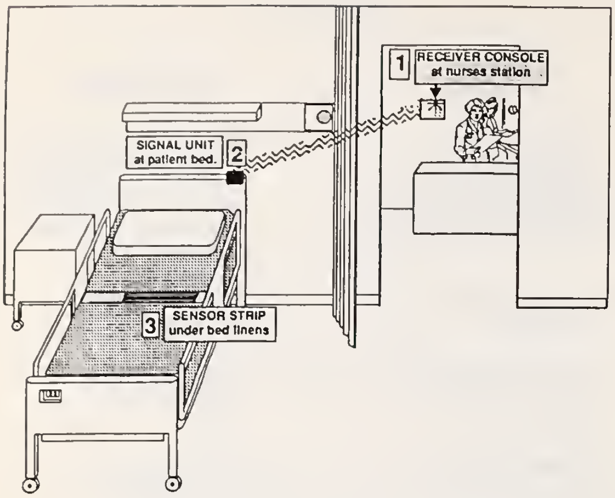
1 RECEIVER CONSOLE at nurses station
SIGNAL UNIT at patient bed. 2
3 SENSOR STRIP under bed linens

Fig. 2. The RN + OnCall bed monitoring system.

and were taking medications (sedatives, antidepressants, antipsychotics) that contributed to poor bed mobility either in isolation or in combination with inadequate bed design, including elevated bed height, unsupportive mattress, unstable bed wheels, slippery floor surfaces.

During the nine-month evaluation period, a total of 24 falls occurred on the unit. The study population had a total of 17 falls (**Table 1**). The experimental group experienced a total of 5 falls: 1 fall from bed and 4 occurring during ambulation or while transferring from chair or toilet. In comparison, the control group had a total of 12 falls: 4 from bed and 8 occurring elsewhere. There was no significant difference in the number of bed falls between the two groups ($p = 1.00$). None of the falls in the study population resulted in physical injury.

Although the use of mechanical restraints and side rails was similar for both groups, in the experimental group the utilization of mechanical restraints to guard against bed falls declined. Mechanical restraints in this group were mostly employed to prevent patients from tampering with intravenous lines and urinary catheters and to protect against falls when patients were out of bed (sitting in a chair).

TABLE 1

Falls Occurring in the Study and Nonstudy Population, 9-Month Evaluation Period of a Bed Alarm System

	Bed falls	Other falls*	Total
Experimental group (n = 35)	1	4	5
Control group (n = 35)	4	8	12
Nonstudy group (n = 225)	5	2	7
Total	10	14	24

* During ambulation and transfers from a chair or toilet.

The experimental group utilized the system for a total of 4,425 h, during which time a total of 143 alarms occurred. Of these, 120 alarms (84%) were true and 23 alarms (16%) were categorized as false. Malposition of the pressure sensor pad—at the patient's shoulder level rather than underneath the buttocks—accounted for 14 (64%) of the false alarms; reasons for the remaining 9 false alarms (36%) are unclear.

Nurses were able to respond to 92% of the alarm activations in less than 1 min (**Table 2**). Eight alarms were answered either in 1–3 min or in more than 3 min. The response time was not indicated for 3 alarms.

Toileting or need to go to the bathroom was the most common reason for transferring out of bed and accounted for 78 (65%) of the true alarm responses (**Table 3**). In 8 cases, the patient was acutely ill or complained of pain, and in the remaining 34 instances, either patients were unable to communicate their reasons for getting up from bed because of confusion or aphasia or the reasons for alarm activation were unaccounted for. Half of all patients attempting a bed transfer after an alarm response were found to be either sitting on the edge of the bed or climbing over the side rail. In the remaining instances, patients were found either standing by the bedside (20%), in the bathroom (15%), or in the hallway (15%).

The alarm system was not associated with any documented bodily harm to patients, nor did the devices interfere with medical and nursing care. Patients, family members, and nursing staff universally approved the use of the system, and several commented that using it was preferable to using mechanical restraints.

Discussion

Bed alarm systems have been designed and are utilized for one purpose: to prevent bed falls. Toward this end, the effectiveness of a system can be measured against several outcomes: the reliable operation of the devices in alerting nursing staff when patients at risk of falling are participating in independent bed transfers; nurses' response time in attending to the patient after an alarm activation; and the extent to which use of an alarm system decreases bed falls.

Operation of the Bed Alarms. In all cases, the system functioned properly, activating an alarm when pressure was removed from the sensor pad. Nurses found the system to be user friendly, easy to install and operate and remaining trouble free. The occurrence of false alarms was the only factor that frustrated nurses and inhibited use of the system. Staff removed the bed alarm from one patient and replaced it with mechanical restraints. When false alarms were due to the malpositioning of the sensor pad underneath the patient's shoulder level, the sensor pad was repositioned underneath the patient's buttock to eliminate any further false alarms.

Nurse Response Time. Aside from one case, nurses were able to respond to patients in a timely fashion to avoid a fall, and they felt that they had sufficient time to do so. In the one exception where a bed fall did occur, the nurse's response time was recorded as greater than three minutes. The circumstances surrounding this episode are unknown, but the event demonstrates that these systems are only as effective in guarding against bed falls as the nurse's response time. The type of system used in this study may have influenced nurse response times. The RN+ On-Call bed monitoring system has a separate console located at the nurses' station for observing alarms, as opposed to other models that operate directly through the nursing call monitor. The nurses may have been more attuned to respond to alarm activations that originated from this separate console and not from the nurse call system.

Bed Falls. The lack of statistical difference in bed falls of system users and nonusers was unexpected but not totally surprising. During the study period, both the experimental and control groups sustained a low rate of bed falls. Consequently, a failure to detect significance may be a result of small sample size, rather than a function of the system itself. Perhaps if a larger study population had been recruited or if a greater number of bed falls had occurred, a positive association between the use of the system and decreased bed falls might have emerged.

An examination of fall occurrences in patients excluded from the study group because they did not meet inclusion criteria lends some support to this hypothesis. A total of seven falls were experienced by this group, of which five were bed falls (Table 1). A comparison of bed falls in the experimental group ($n = 1$) and in the combined control and nonstudy groups ($n = 9$) showed a greater propensity to fall from bed in patients not using the system. Although the difference did not reach statistical significance ($p = 0.3577$), it does demonstrate an association between an increase in sample size and bed falls in patients not using the system. Whether the patients in the nonstudy group were at increased risk for bed falls at the time, which might have been prevented by a bed alarm, is unknown.

TABLE 2
Nurse Response Time to Alarm Activations, 9-Month Evaluation Period of a Bed Alarm System

	Number (%)
Less than 1 min	132 (92)
1–3 min	5 (4)
More than 3 min	3 (2)
Unknown*	3 (2)
Total	143 (100)

* Response time not recorded.

However, other explanations are possible. First, the low incidence of bed falls in the study population may reflect greater nursing and medical effort to prevent falls in patients assumed to be at high risk of falling. To prevent potential falls, nurses hourly observed both groups of patients while patients were in bed and provided assistance with transfers. There is the potential for bias introduced by the nurses' awareness of the intervention and perhaps by their anticipation of the goals of the study (the Hawthorne effect). The nurses' knowledge of patients being included in the study may have caused them to change their behavior toward the prevention of bed falls. Also, physicians assigned to the unit are geriatric fellows-in-training and geriatric attendings who are more likely to search for modifiable fall risk factors. A similar study on a general medical unit, where nurses and physicians may not be as focused on fall prevention, might yield a greater sample size and significant findings. It might also help to explain the low rate of bed falls found in this study.

Second, the low rate of bed falls in the control group may reflect an increased use of mechanical restraints, applied either after the first fall or as a precaution in patients observed to be participating in unassisted transfers. Anecdotal nursing reports and retrospective chart reviews suggest that possibility, but data are insufficient to truly support it.

A third possibility is that the use of side rails may have influenced bed fall rates. In both the experimental and control groups, half side-rails were universally employed as a fall preventive measure. While previous research has noted an association between the use of bed side-rails and increased fall risk (3), in some instances side rails may prevent falls. For example, we observed several patients with poor bed mobility use the half side-rail to safely transfer from bed, suggesting that a partial side-rail may actually be used as a

TABLE 3
Reasons for True Alarms, 9-Month Evaluation of a Bed Alarm System

	Number (%)
Toileting	78 (65)
Acute illness	8 (7)
Unknown	34 (28)
Total	120 (100)

falls preventive, a subject worthy of further research.

Finally, the low fall rate may indicate that patients with poor bed mobility either restrict their number of bed transfers or call for assistance through the nurse call system (available by the bedside). However, this hypothesis is contradicted in part by the large number of true alarm system activations ($n = 120$) that occurred. Whether the two groups of patients used the nurse call system prior to exiting from the bed is not known.

Efficacy of the Alarm System. Despite the low rate of bed falls and lack of significant findings, evidence supports the efficacy of the alarm system. A comparison of users and nonusers demonstrated a clinical trend toward decreased bed falls. In addition, the 120 true alarm activations that occurred in patients using the system represented potential bed falls that were avoided, with the exception of one fall. Also, a bed alarm system may protect against physical injury, because one hip fracture occurred in the nonstudy group as a result of a bed fall, and one patient in the control group had a mechanical restraint complication; the patient was found dangling by the bedside with the vest restraint attached.

In addition to a reduction in bed falls, the experimental group exhibited a clinical trend toward decreased falls when out of bed. A comparison of falls in the experimental and the control group (Table 1) shows that patients using the system had fewer falls ($n = 4$) while engaging in out-of-bed activities than patients not on the system ($n = 8$). Although the difference is not great, it suggests that the system was protective in alerting nurses that patients were getting out of bed; it also allowed the nurses to provide assistance for out-of-bed activities. This is supported by the circumstances surrounding the falls in each group. In the control group, the falls originated shortly after the patient left the bed. Consequently, the nurses were not alerted ahead of time when patients were engaging in out-of-bed activities, and nurses were unable to offer assistance. With the experimental group, the falls occurred well after the patients had left the bed, originating while walking or while transferring from chair or toilet. These falls could not have been avoided with the use of a bed alarm.

A tendency of the control and nonstudy groups toward more falls raises the possibility that observing patients hourly may not be helpful in preventing falls. If future research supports this assumption, then the use of nurses' time might be better spent in performing other duties important to patient care. This also suggests that bed alarms may be a suitable alternative to frequent patient observations by the staff and thereby result in considerable cost savings for the institution.

Potential Uses of Bed Alarms. Apart from preventing falls, the findings suggest that bed alarms may be beneficial in other ways. They may be valuable in helping monitor clinical change in patients. Eighty-three percent of the true alarm responses were for either toileting (frequent urination, nocturia) or acute illness (congestive heart failure, chest pain), suggesting that using a bed alarm to alert staff to changes in the patient's medical condition may result not only in more rapid interventions, but also in reduction of risk for falling. For example, nocturia has been found to be a risk factor for falls (8) and in some instances is an early indication of congestive heart failure. If patients are treated at an early stage, the frank onset of heart failure and the likelihood of falling may be avoidable. Also, attending to patients who require frequent toileting in a timely fashion may reduce both the risk of falls and episodes of incontinence.

Summary

Bed alarms are an acceptable method of fall prevention. The use of an alarm system for patients at risk of falling resulted in a clinical tendency toward a decrease in falls from bed and falls during out-of-bed activities. In addition, such alarm systems may help reduce the use of mechanical restraints and the frequency of nurse monitoring to prevent bed falls. Bed alarms may also be useful in monitoring clinical changes in certain patients. The alarms were not associated with any adverse patient effects, nor did they interfere with patient care. The attitudes of patients, family members, and nurses toward the utilization of an alarm system were positive.

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Geropsychology and Neuropsychological Testing:

Role in Evaluation and Treatment of Patients with Dementia

Rajendra Jutagir, Ph.D.

Dementia is a condition of global cognitive deterioration that is not due to clouding of consciousness. A diagnosis is made by demonstrating impairment in short- and long-term memory, accompanied by impairment in at least one additional area of higher cortical function (language, conceptualization), or personality change. Impairment must be sufficient to interfere with work or social activities. Progressive decline in cognitive functions would suggest Alzheimer's disease (1).

The Work Group established by the National Institute of Neurological and Communicative Disorders and Stroke and the Alzheimer's Disease and Related Disorders Association recommended neuropsychological assessment to assist in the diagnosis of Alzheimer's disease (2). Neuropsychological testing establishes whether the degree of a patient's cognitive loss exceeds what one would expect from normal aging. Apart from identifying specific cognitive deficits, such testing results in a profile of relative strengths and weaknesses. This can confirm whether deficits are global or focal, and helps differentiate between a variety of dementing disorders. In addition, testing provides a baseline against which it is possible, by subsequent retesting, to document whether a patient's cognitive capacity has progressively declined with time.

The psychologist working with older adults encounters the same variety of mental disorders as in younger adults, and utilizes similar (though sometimes modified) treatments (3). However, dementia has a higher prevalence in the older group, and is a source of such disability and anguish that it warrants special emphasis.

Although there is a tendency to neglect patients with dementia syndromes, who are often seen as untreatable (4), a broad array of interventions is available. Patients may be only mildly impaired for several years, during which time they can engage productively in high-level interventions such as psychotherapy. With modification of technique, psychotherapy can be conducted even into the moderate stages of dementia. Apart from psychotherapy, there are numerous psychosocial interventions. Treatment is also available to caregivers of demented individuals; by reducing stress and promoting understanding, such treatment can considerably enhance the quality of life of the patient.

The objectives here are to review the role of neuropsychological testing in the evaluation of dementia; and to examine psychotherapy and psychosocial treatments for demented individuals and their families, with emphasis on a psychoeducational approach.

Neuropsychological Assessment

Disease processes in dementia produce changes in the brain. A neuropsychological test battery is administered to the patient to develop a profile of cognitive functions, which is used to make inferences about changes that have occurred in brain structures.

A thorough test battery would assess the following cognitive functions: memory, attention, language, conceptualization, visuospatial and frontal systems functions. Recent memory is

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tested by presenting the patient with verbal stimuli (stories, wordlists) or visual stimuli (designs, objects) and having the patient recall them. Ability to learn new information is documented by examining performance over repeated trials of a memory task, which should show a learning curve. After a delay of 20–30 minutes, the patient is asked to recall stimuli learned earlier, which would demonstrate whether there has been excessive decay in the material learned. Remote memory can be tested by asking about verifiable historical data (for example, the name of the president during World War II). The modality of test administration (verbal, visual) can be selected to compensate for sensory impairment, which is a common problem in the elderly. For patients with speech deficits, recognition testing and tests not requiring oral responses are used. Methods of testing memory and other cognitive functions in the elderly are reviewed in greater depth elsewhere (5).

The Neuropsychological Profile and Its Uses. The patient's neuropsychological profile would be established by comparing performance on these tests to established norms for the patient's age group, and charting areas of strength and weakness. Even when test results fall within the norms, performance may be impaired in relation to the level of the individual's own premorbid functioning. Educational and occupational achievement may assist in clarifying this situation.

This neuropsychological profile, consisting of the level of performance in different areas of cognitive functioning, is examined to arrive at a diagnosis. To characterize a dementia, global deterioration would have to be documented by impairment in memory and at least one other cognitive ability. In Alzheimer's disease one would further expect poor delayed recall, a strong indication of anterograde amnesia. Global impairment with prominent frontal features, including poor executive abilities and disinhibition, might suggest Pick's disease (6). Yet another profile, one that includes cognitive slowing and poor manipulation of information, might suggest a subcortical dementing process (7). Often enough it is not possible to clearly characterize the dementia.

Other disorders may be diagnosed from the profile. One might suspect a focal lesion if, for example, the patient is anomic but otherwise cognitively intact, or if the primary findings are impairment in attention and conceptualization. Patients with delirium would be expected to have attentional deficits shown by impairment on memory span and vigilance tasks. This is often sufficiently pronounced to prompt discontinuation of memory testing, since it calls into question such patients' ability to register stimuli presented to them. Disorientation would also be expected in this disorder. In diagnosing pseudodementia, qualitative aspects of testing play an important role. One would look for inconsistencies in testing, such as better performance on difficult than on easy items. Because mild depression is unlikely to manifest itself in significant cognitive loss, mood would have to be quite depressed for this diagnosis to be made.

Distinguishing whether change in cognitive functioning is due to normal aging or to a disease process is particularly difficult in early or mild dementia, and screening instruments often lack sensitivity in these cases. Thus patients who repeatedly complain of memory loss or other cognitive difficulties may have scores within normal limits on typical screening tests for dementia. These patients should be diagnosed with in-depth neuropsychological testing, which is probably the most sensitive method of making this discrimination.

It is of course insufficient to know only that the patient is demented. To clarify the etiology of the dementia, the full array of causes must be addressed. Medical examination to rule out infections, toxic or metabolic problems, and other neurological involvement is a necessary part of the diagnostic procedure. A brain scan is often helpful to rule out tumors, hydrocephalus, and stroke activity. Once these possibilities are eliminated, Alzheimer's disease and multi-infarct dementia are the most likely causes of global cognitive impairment in the elderly.

Interventions

The First Intervention: Review of Findings. A critical moment in the care of the elderly demented patient occurs immediately following evaluation, when the provider and patient meet to review the findings. Although rarely discussed in the literature, this contact is of considerable importance. It should be viewed as the first intervention, because it lays the groundwork for later interventions. The diagnosis is best presented by a professional who has established a relationship with the patient, to whom the patient can turn for future care.

Since some causes of dementia are potentially reversible, the case for early detection is clear. However, there is some debate about the wisdom of telling patients their diagnosis when they have an irreversible dementia, Alzheimer's disease in particular (8). Arguing against disclosure is the uncertainty of the diagnosis, the perceived paucity of therapeutic options, and the fear that the stress of the diagnosis may exacerbate the patient's symptoms. In favor of disclosure is the right to self-determination, and the need for full participation in formulating advance directives, financial planning, and other personal affairs while the patient is still competent to express herself or himself. I take the position that frankness in disclosing the diagnosis is generally in the patient's best interest, promoting both self-determination and confidence in the health-care provider.

Clinical judgment on the patient's mental status should determine how the diagnosis is presented. Many patients come to the evaluation already apprehensive of the possibility of Alzheimer's disease. On those occasions when it is confirmed, these patients may not be excessively surprised. At the least, patients can tolerate learning that they show some signs of cognitive impairment which should be followed in the months ahead to document whether it progresses. This approach is helpful with very anxious or depressed patients, with whom a treatment alliance can be formed which will later allow deeper exploration of their symptoms and diagnosis. If the patient is acutely emotionally disturbed, it may be preferable to discontinue testing or withhold the findings until the patient has been stabilized, or to complete the evaluation on an inpatient basis.

Psychotherapy. Psychotherapy can help the dementing patient with the immediate tasks of adjusting to the diagnosis and becoming engaged in planning for the future. Treatment necessarily includes a psychoeducational component. Thus the professional provides information about the diagnosis and the disease, and makes recommendations, while simultaneously responding to the patient's emotional reactions and mobilization of defenses. When the diagnosis is made early in the dementing process, long-term psychotherapy is also feasible for some patients. Deeper psychodynamic exploration of the personality structure and defenses can help the patient come to terms with unresolved life conflicts.

Psychotherapy must be adapted to the stage of the disease (9). With progression there is increased emphasis on loss of function. Having someone to discuss this with is reassuring to the patient and can lead to better coping with deficits. The therapist may have to be empathic in verbalizing the patient's feelings as self-expression diminishes. Still later, reality testing may become compromised, with evidence of delusions or hallucinations. It can reduce a patient's anxiety to know that certain experiences are merely the product of difficulty interpreting reality. For example, one patient stated that he knew that the bomb next to his bed was probably not real; instead of becoming agitated and trying to flee the bedroom, he turned over and went back to sleep. Psychopharmacologic methods become increasingly necessary in this stage of the disorder.

Psychoeducational Treatment for Family Members. Some aspects of family psychoeducational treatment developed for mental illness (10) can be adapted for use with the families of dementia patients. Examining how family members react to the patient's symptoms can help to manage stresses of caregiving and minimize family burden. The professional also serves an important educational function. What is dementia? What tests were done and what did they show? What are the implications for the future? Will the patient have to go to a nursing home? Will the disease be inherited by family members? These questions are commonly raised by families and can be addressed in this context. Structured recommendations regarding future planning and use of respite or home aides can also be made and clarified. Providing continuity of care is critical so that the family feels supported and knows where to turn for help. Given the multiple needs of the demented patient, the establishment of a treatment team is helpful in ensuring that the patient receives comprehensive care. Even in private practice it is possible to establish relationships with health-care providers in other disciplines who, through consultations and referrals, can serve as a team. Finally, connecting family members with a support network, including groups and social agencies, helps to reduce isolation and the sense of enduring difficult times alone (11).

Conceptualizing dementia as a chronic mental illness may put the disorder into perspective for the health-care provider. In one view (12), families must adapt to chronic mental illness in three primary areas: interpersonal, instrumental, and life course. Interpersonally, many feelings are aroused between the patient and family members. The latter may express anger toward the patient because of his or her behavior, thinking that the patient could perform normally by trying harder. Their anger may be exacerbated by feeling frustrated and let down by the health care system that often fails to diagnose dementia adequately, or to provide adequate support. The therapist can address family anger by clarifying that the patient is functioning as well as he or she can, which may require providing concrete evidence of organic dysfunction in the form of test results. If the disease progresses, mourning the loss of the person they knew becomes increasingly important. Since patients often remain physically healthy while their personality disintegrates under the onslaught of the disease process, families may not readily become aware of their sense of loss and the emotions that accompany it. The therapist can clarify the situation and help the family accept this loss.

Instrumentally, the family has to adapt to problems related to the patient's behavior. A major source of burden to dementia caregivers is the daily difficulty in functioning (losing things, inability to get dressed), and problem behaviors (wandering, combativeness). The therapist can make practical suggestions about how to deal with these, while at the same time exploring aspects of the caregiver's circumstances or personality that make certain behaviors particularly difficult to cope with.

Finally, life-course issues are raised because patients can live for many years with a dementia. A common pattern is for a close family member to become completely consumed by the caregiving task. With support and planning, the disease process can become better integrated into family life so that it does not demand the end of a normal existence for this person. Family treatment can explore family resources, build a sense of perspective with regard to the disease, and engender optimism in family members who may have felt that they were unable to go on.

Summary

Cognitive loss in the aged should be evaluated as early as possible, since some causes of impairment may be reversible. Neuropsychological testing is probably the most sensitive method of detecting early or mild dementia. On completion of the evaluation, the first meeting with the patient and family is critical in laying the groundwork for subsequent interventions. Frankness in discussing the diagnosis of dementia is advocated, as it facilitates patient self-determination and enhances confidence in the health-care provider. Interventions, including psychotherapy, are presented in a psychoeducational framework, where the aim is to provide information to the patient and/or family while monitoring and responding to emotional reactions and defenses. Conceptualizing dementia as a chronic mental illness may be helpful to the health-care provider. Although there is no cure for Alzheimer's disease or for multi-infarct dementia, treatments are available in the psychological and psychosocial domain. These have enormous potential for alleviating suffering and improving the quality of life of patients and their families, and therefore should not be overlooked.

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Clinical Evaluation of Dementia

Jonathan Koblenzer, M.D.

THIS ARTICLE describes an approach to the clinical diagnosis of the patient with possible dementia. For both theoretical and practical reasons, these patients pose special conceptual problems for the clinician. For one thing, mental phenomena are intangible and therefore hard to define and quantify. Cardinal clinical phenomena such as mood and affect, abstract thought and judgment—and even more specific cortical functions such as agnosia and the apraxias—do not have uniformly accepted definitions. Clinicians can differ dramatically, depending on their education and specialty training, in how they define these phenomena (1, pp. 391–405; 2, pp. 19–44). It is not surprising that bedside clinical methods of determining a patient's mental state are similarly variable (3), or that clinical syndromes can be defined and ordered in different and overlapping ways (1, pp. 103–107; 2, pp. 1–18).

Multiplicity is promoted because any mental syndrome, including dementia, can be associated with a great number of different diseases and pathologic processes. Dementia is a clinical diagnosis based on finding impairment in a number of functions of the mind. These impairments can only be found in a clinical interview. Abnormal blood tests and scans do not make the diagnosis of dementia. There are no biologic markers diagnostic of the dementia syndrome; conversely, there are no mental symptoms pathognomonic of a particular dementing disease process in the brain. More practically, our knowledge of brain functioning in relation to mental events in health and disease is growing explosively, so that all current knowledge has a provisional quality.

Two strategies have been developed over the last 30 years to address these issues. The first is the development of a standardized descriptive language of psychiatry, as well as operationalized, criterion-based psychiatric diagnosis as embodied in the *Diagnostic and Statistical Manual of Mental Disorders,* of which the third revised edition (DSM-III-R) is the latest (1, pp. 103–107). Thus the diagnostic inclusion and exclusion criteria that define a disorder are explicitly listed. The modified Jones criteria for acute rheumatic fever are an example from another field of medicine (4).

The second strategy is the development of standardized questionnaires, such as the Mini-Mental State Exam (MMSE) (5) or the Hamilton Depression Scale (6), that quantify the intensity of mental symptoms. Of note, instruments like the MMSE are best used to quantify symptoms in previously diagnosed patients and do not replace diagnostic tools such as DSM-III-R.

Definitions

Several definitions of the dementia syndrome have been published and are used clinically (1, pp. 103–107; 2, pp. 1–18). An ideal definition would combine maximum diagnostic sensitivity and specificity with ease of use. Unfortunately, no such definition has been developed. The DSM-III-R criteria (1, pp. 103–107) **(ruled box 1)**, though not universally accepted (2, pp. 1–18), are easy to use and have been shown to be reliable (7).

The cardinal symptoms of dementia are short- and long-term memory loss. By definition, memory is always impaired in dementia. Short-term memory is tested by asking the patient to repeat three unrelated words five minutes after being presented with them. Long-term memory can be more difficult to test; the results often require corroboration from the family or friends of the patient. This is particularly important in Alzheimer's disease (AD), where patients can main-

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tain the appearance of good social functioning until quite late in their illness.

By definition, memory disturbance must be accompanied by at least one other type of cognitive impairment; often it is associated with several. Abstraction, which can be defined as thinking in terms of categories rather than specifics (8), can be tested by eliciting interpretations of proverbs; responses may be abstract or concrete. A concrete interpretation of the proverb "Don't cry over spilt milk," for example, is that milk is easily cleaned up or that more can be bought at the store. A more abstract response is that past events are irrevocable, cannot be influenced by present wishes, and are therefore not worth worrying about.

Judgments are global evaluations of a situation, with a view to possible actions (9). Judgment is best evaluated by assessing the patient's ability to perform day-to-day responsibilities, information usually readily available from the history. Actions such as giving money away to strangers or disrobing in public are not uncommon examples of impaired judgment in patients with dementia.

Aphasias, constructional and ideomotor apraxias, and agnosia are symptoms that attend damage to specific cortical areas. The best way to define and test some of these functions remains controversial (2, pp. 19–44; 3). Broadly speaking, these symptoms can be evaluated thus: aphasia, by asking a patient to repeat a sentence; constructional apraxia, asking for a copy of a figure; ideomotor apraxia, asking a patient to follow a command; and agnosia, asking patient to recognize and name common objects. These tests are all part of the MMSE.

Personality comprises the stable and predictable patterns of reaction to and experience of life events. Personality traits are usually established by adolescence; change in personality is an important sign that can be associated with dementia.

DSM-III-R criteria require that any cognitive deficits significantly interfere with social and vocational functioning. Again, this is usually evident from a well-taken history. In addition, various functional scales, such as the Instrumental Activities of Daily Living Scale (IADLS) (10), can help quantify the degree of overall functional impairment. Of note, there is evidence of a correlation between degree of cognitive impairment on the MMSE and performance in IADLS (11).

Ruling out delirium is crucially important. Delirium is the "great mimic" of psychiatry and, by definition, has an often reversible organic cause. A delirious patient can have a wide variety of psychiatric syndromes, including dementia, but delirium is usually not present in patients who are able to attend (1, pp. 100–103), which can be tested by asking the patient to immediately repeat a series of digits presented at one-second intervals. Any patient who can repeat five digits or more is determined to be attentive (2, pp. 21–24) and delirium is not likely. Inattention, defined as inability to repeat five digits, has a wide differential diagnosis, including delirium, mania, depression, anxiety, and psychosis. Making a syndromal diagnosis in the elderly inattentive patient can be extremely difficult.

1. **Diagnostic Criteria for Dementia (*Diagnostic and Statistical Manual of Mental Disorders* *3rd rev. ed.*)**
   - A. Demonstrable evidence of impairment in short- and long-term memory.
   - B. At least one of the following:
     - (1) impairment in abstract thinking
     - (2) impaired judgment
     - (3) other disturbances of higher cortical function, such as aphasia, apraxia, agnosia, and "constructional difficulty" (constructional apraxia)
     - (4) personality change (i.e., alteration or accentuation of premorbid traits)
   - C. The disturbance in A and B significantly interferes with work or usual social functioning.
   - D. Not occurring exclusively during the course of delirium.
   - E. Either (1) or (2):
     - (1) There is evidence from history, physical examination, laboratory tests of a specific organic factor judged to be etiologically related to the disturbance.
     - (2) In the absence of such evidence, an etiological organic factor can be presumed if the disturbance cannot be accounted for by any nonorganic mental disorder (e.g., major depression accounting for cognitive impairment).

Reprinted with permission from DSM-III-R, p. 107.

Finally, there must be at least presumptive evidence of an organic etiology of the dementia syndrome (**ruled box** 2).

A great virtue of these criteria is that a diagnosis can usually be made quickly at the bedside. Properly used, instruments such as the MMSE and the Global Deterioration Scale (GDS) (12) can help make the diagnosis of dementia and at the same time quantify its severity. Folstein et al. found that MMSE scores of 23 or less were predictive of the presence of a dementing process (5) and that the scores varied with the severity of functional impairment. Modified criteria using DSM-III, the predecessor to DSM-III-R, have had a positive predictive value of 82%–90% in patients with Alzheimer's disease (13). On the other hand, these criteria are insensitive for clinical signs of early dementia (14). The results of screening tests, such as the MMSE and the GDS, must be interpreted with caution. Sensory deficits, such as hearing and visual loss, aphasias, and educational level, can all confound the interpretation of results.

2. Classification of Some Common Causes of Dementia

Degenerative dementias
- Alzheimer's disease
- Pick's disease
- Parkinson's disease
- Huntington's disease

Vascular dementias

Viral dementias
- HIV-1 encephalopathy
- Progressive multifocal leukoencephalopathy
- Jakob-Creutzfeld disease

Bacterial dementias
- Neurosyphilis
- Lyme disease

Metabolic dementias
- Vitamin deficiency
  - B_{12}, folate
  - Thiamine
  - Niacin
- Endocrinopathy
  - Hypothyroidism
  - Hypoglycemia
  - Hyperparathyroidism
- Heavy metal intoxication
- Alcohol and drug abuse
- Prescription and nonprescription drugs (e.g., psychotropics)
- Uremia
- Liver failure
- Chronic obstructive pulmonary disease
- Congestive heart failure

Hydrocephalus

Trauma

Space-occupying lesions
- Subdural hematomas
- Tumors

Adapted from ref. 38.

Etiology

There are a number of causes of the dementia syndrome (ruled box 2), but in Western countries most cases are associated with either Alzheimer's disease (22%–70%) or multi-infarct dementia (MID) (8%–47%) (2, pp. 5–8; 15); other cases are caused by a variety of conditions. The marked variability is most likely due to selection bias in the studies, differences in diagnostic criteria, and the practical difficulty in making an absolutely definitive diagnosis of dementia. In the following section, common or otherwise important (e.g., reversible) etiologies and their presentations are discussed.

Alzheimer's Disease. AD is characterized by a progressive, steady decline in cognitive functioning beginning in mid-to-late life. Memory dysfunction and word-finding problems are early symptoms, along with poor judgment and disorientation to place. Impaired performance of delayed visual and verbal recall tasks is a sensitive sign of early dementia (16). As the disease progresses, fluent aphasia supervenes, with worsening memory and disorientation. Psychiatric manifestations, such as depression, psychosis, and personality change (usually irritability), as well as agitation and wandering behaviors, may appear in as many as 90% of AD patients (17). Late AD is characterized by severely impaired cognition, mutism, incontinence, and agitation. Contractures, seizures, infections, and coma supervene in the terminal phase. The prevalence of AD is highly correlated with age, varying from a rate of 4.4/100,000 in people under 60 to 1431.7/100,000 in those over 80 (18).

The diagnosis of AD is made by excluding other possible causes of dementia (1, pp. 119–121) (see below). In the living patient, it is not feasible at present to exclude all other etiologies of dementia, so there is usually a degree of uncertainty in the clinical diagnosis. One set of diagnostic criteria, developed by the National

Institute of Neurological and Communicative Disorders and Stroke and the Alzheimer's Disease and Related Disorders Association Work Group (19), reflects this by labeling patients as having "possible," "probable," or "definite" AD, depending on the available clinical evidence. Characteristic neuropathologic findings on biopsy or autopsy material are required for the latter diagnosis.

Multi-Infarct Dementia. In contrast to the steady and progressive onset of Alzheimer's disease, MID is characterized by abrupt and stepwise appearance of the symptoms of the dementia syndrome (1, pp. 121–123), along with evidence of stroke or lateralizing neurologic signs and a patchy distribution of deficit. Some mental functions are preserved quite well, whereas others are significantly impaired. The presence of conditions that are risk factors for cerebrovascular disease, such as atrial fibrillation, diabetes mellitus, or hypertension, supports the diagnosis. Evidence of infarcts on computed tomography or magnetic resonance imaging is confirmatory. MID comprises a heterogeneous group of conditions, including large- and small-vessel thrombotic and embolic disease (2, pp. 170–171). Also in contrast to Alzheimer's disease, MID occurs in younger patients and affects men more than women (20).

Alzheimer's Disease and Multi-Infarct Dementia. One autopsy study showed that MID and AD coexisted in about 20% of dementia patients (21), not an unexpected finding in view of the frequency of each of these conditions. Mixed dementia of this type is suspected when a patient evidences features of each. Common scenarios include the patient with progressive onset of dementia and a few lacunar infarcts on imaging tests, or a patient with a cognitive impairment that seems disproportionate to the size and location of an infarct.

Parkinson's Disease. A mild-to-moderate dementia can occur in 15%–20% of patients with Parkinson's disease (22), characterized by impoverishment and slowing of the cognitive processes, concreteness, and indecisiveness; predominantly cortical functions, such as speech, are usually spared. This combination of symptoms has been described as a subcortical dementia (23). It is important to rule out depression, which can occur in 40%–60% of patients with Parkinson's disease (24) and can mimic a dementing process ("pseudodementia").

"Reversible" Dementias. Among the dementias accounted as reversible are the more common dementing processes for which some evidence exists that the initiation of a specific treatment will halt or even reverse the progression of the disease, making the diagnosis of these conditions particularly important. On the other hand, it is debatable how reversible some of these dementias truly are (25), since the number of cases studied is relatively small and there are often confounding variables in the case reports. In addition, some treatments are invasive and attended by some risk of complications.

Vitamin B_{12} deficiency can be associated with dementia and depression in the absence of anemia (26). The dementia is often associated with subacute combined degeneration of the spinal cord. Treatment with parenteral vitamin B_{12} can induce more or less complete recovery occurring in days to weeks. Rarely, folate deficiency produces a similar clinical picture (27).

Slowed cognition is not uncommon in patients who have significant hypothyroidism. More rarely, the clinical picture can progress to frank dementia or delirium with delusions and hallucinations (28). Partial or complete reversal of these syndromes is possible with thyroid replacement.

Neurosyphilis was formerly a common cause of institutionalization for dementia and psychosis, usually 20 years after the initial infection. Delusions of grandeur associated with dementia, affective instability, and hallucinations were all part of the clinical picture. In the antibiotic era this classic picture is rare, because many patients are exposed to antibiotics during the course of their illness (29). Instead, patients may offer a nonspecific picture of dementia associated with gradual loss of vision, loss of ankle jerks, and abnormalities of the pupillary responses, among other signs.

Normal-pressure hydrocephalus, first described in 1965 (30), is suspected in patients with the clinical triad of dementia, gait disturbance (apraxic or "magnetic" gait), and incontinence, and in whom neuroimaging reveals lateral ventricles enlarged out of proportion to sulcal size. Ventricular shunts can dramatically relieve symptoms in these patients. Serial lumbar punctures have been used to select patients for this procedure (31).

Chronic subdural hematoma can attain large size and remain asymptomatic; not uncommonly, it is associated with the dementia syndrome (32). Delirium and focal neurologic findings can both supervene.

Miscellaneous. Pick's disease, Huntington's disease, and Jakob-Creutzfeld disease are three uncommon dementing illnesses that are noteworthy because of their often striking clinical pictures. It is beyond the scope of this article to discuss them, but any clinician evaluating patients with dementia needs to be familiar with their diagnosis.

Differential Diagnosis

Despite the unambiguous diagnostic criteria for dementia, it can be hard to distinguish patients with dementia from those with delirium, those with the primary "functional" disorders of depression or psychosis, and those with focal cortical deficits, such as aphasia or amnesia.

Delirium is common in elderly patients, particularly those with dementia; in addition, delirium can itself mimic dementia almost exactly. As mentioned above, the presence of distractability (1, pp. 100–103), or inattention, can distinguish between the two entities. In the inattentive patient who appears demented, every effort to identify the common causes of delirium must be made because treatments are usually available. In elderly patients, these causes are most commonly drug toxicities, infections, and metabolic and electrolyte disturbances (33). Administration of all unnecessary medications should be discontinued, and doses of necessary drugs should be reduced to a minimum. Often this is sufficient to clarify the picture, but sometimes only after several weeks of drug washout.

If there is no evidence of other likely causes of delirium, an electroencephalogram (EEG) is sometimes helpful. The diffuse slowing of the predominant rhythms that often occurs in delirium is not as common in mild dementia or in functional illness in the elderly. If the EEG is normal, the inattention may be due to psychiatric syndromes, such as anxiety, depression, mania, hallucinations, or formal thought disorder. These syndromes may occur independently of the dementing process or be a consequence of it. In these cases, consultation with a geriatric psychiatrist can be helpful in clarifying the diagnosis.

In addition to causing inattention in the patient with dementia, depression and psychosis can, like delirium, mimic dementia itself. Some depressed patients can, in all respects, look demented (34); with treatment this picture remits. Clinical criteria for distinguishing "pseudodementia" of depression from dementia proper have been proposed (34). However, the positive and negative predictive values of these criteria are not known. The recent onset of neurovegetative signs of depression, such as sleep and appetite disturbance or psychomotor agitation, may be helpful in making the diagnosis. Often the clinical distinction is difficult, and consultation with a geriatric psychiatrist can help clarify the diagnosis. Recent work suggests that "pseudodementia" may be a herald of dementia proper (35).

Similarly, some patients with schizophrenic illnesses may appear to be demented, especially if they evidence extreme social withdrawal, mutism, catatonia, or a severe formal thought disorder. Again, psychiatric consultation may be helpful.

Aphasia and amnesia may be components of the dementia syndrome but are not in themselves sufficient to make the diagnosis. Patients with these conditions are often incorrectly diagnosed, either because they are severely disoriented due to amnesia or because they have difficulty communicating due to their aphasia. A careful examination can usually demonstrate that they do not suffer from the more global impairments of dementia.

Diagnosis and Evaluation

The basic strategy in the evaluation and diagnosis of the patient with apparent dementia is to accomplish the following two goals. The first is to identify the psychopathologic features of the patient's illness in order to make a syndromal diagnosis. This depends on a good clinical interview, to distinguish dementia from delirium, depression, or other "functional" or organic psychiatric syndromes (as above). The second goal is to identify the etiology of the dementia syndrome. Here the history, physical examination, and selected laboratory tests and special investigations can be essential. The main reason for making an etiologic diagnosis is to identify either treatable or heredofamilial dementias. In either case, the information obtained can be useful to the patient and his or her family. For example, up to 20% of patients with Alzheimer's disease are reported to have inherited their illness with an autosomal dominant pattern (36).

All patients with suspected dementia need a complete history and physical examination, as the possible causes of dementia are numerous (ruled box 2). The history should focus on the onset of the illness, drug and alcohol exposure, nutritional history, exposure to toxins, heavy metals, or infectious agents, medical illnesses and medication use (including nonprescription medications), and family history of dementia or psychiatric illness. A physical examination, with careful attention to the nervous system, can confirm or reveal the presence of serious systemic or neurologic illness that may explain part or all of the etiology of the dementia.

Laboratory studies should include at least a complete blood cell count, complete chemical screen with liver function tests, urinalysis, measures of vitamin B_{12} and folate levels, serum drug screen, rapid plasma reagin, thyroid function tests, electrocardiogram, chest x-ray, and computerized tomography of the brain (37). This information should suffice to diagnose the vast majority of dementias; further investigation is usually unnecessary. Little current evidence supports routine comprehensive neuropsychologic testing in the differential diagnosis of the dementia syndrome (2, p. 40). Such testing may be diagnostically helpful in patients who have early dementia or atypical clinical features.

Depending on the clinical situation, an electroencephalogram, lumbar puncture, serum heavy metal screens, test for human immunodeficiency virus, and brain biopsy may be helpful, as well as neurologic and psychiatric consultation. If studies for dementia reveal no etiologic cause, the patient most likely has Alzheimer's disease; infarcts suggest multi-infarct dementia or mixed (MID and AD) dementia, and other positive findings suggest a specific etiology or mixed dementia (with Alzheimer's disease), as discussed above.

Summary

The diagnosis of dementia is a clinical one that can only be made with the rigorous use of clearly defined diagnostic criteria in an interview setting. The diagnosis cannot be made by laboratory tests or imaging techniques alone. In the elderly, a number of other psychiatric syndromes must be distinguished from dementia, including delirium, psychosis, depression, and mania. Sometimes it is not possible to make this distinction with confidence.

Most dementias are caused by Alzheimer's disease or multi-infarct dementia, and the probable etiologic diagnosis can be made fairly quickly. However, a number of etiologies are possible, and some patients require extensive study. Some uncertainty is usual in the diagnosis of the living patient because routine brain biopsy is not feasible. Geropsychiatric and neurologic consultants can be helpful in selected cases.

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Osteoporosis in the Aged

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Osteoporosis occurs when bone mineral density decreases to the point that bone fractures in the presence of minimal or no trauma. Clearly, preventing bone loss or attaining optimal peak bone mass as a young adult can minimize susceptibility to this disorder. Early research in osteoporosis emphasized prevention of the rapid bone loss that occurs in the early postmenopausal years. Yet the effects of osteoporosis are felt much later in life. This paper summarizes the evaluation and treatment of elderly women with osteoporosis, drawing on the minimal research on osteoporosis in the elderly.

Epidemiology

Approximately 250,000 hip fractures and 500,000 vertebral fractures occur each year in the United States. The lifetime risk of a hip fracture for a 50-year-old white woman is 15.6%, with a median age for hip fracture of 79 years (1). The lifetime risk of Colles' fracture is 15.0% at 50 years of age, with a median age of 66 years for the fracture. Approximately 32% of 50-year-old white women will experience a vertebral fracture, although Obrant et al. found that only half of all vertebral fractures come to medical attention (2). Twenty-seven percent of 65-year-old and 18.3% of 80-year-old white women can expect to suffer a first vertebral fracture (1). Thus, by and large, elderly women have the disease.

A recent prospective study showed that a decrease in bone mass by two standard deviations from that of a normal 35-year-old conferred a four-to-sixfold increase in risk for vertebral fracture, whereas a single prior vertebral fracture increases risk of recurrence by four-to-fivefold. Compared to women with the highest bone density and no vertebral fractures, women with the lowest bone mass and one fracture were 25 times more likely to fracture during each year of follow-up (3).

Bone Metabolism in Elderly Women

Bone loss rates in elderly women are less than half those in perimenopausal and early postmenopausal women, 1%–1.5% as compared to 2%–3% per year. Although the annual bone loss rate in older women is lower, Nordin et al. estimated that the majority of bone loss between 55 and 75 years of age was due to aging (62%) rather than to menopause (38%) (4). Although some previous studies of bone loss in the elderly showed a slowing of bone loss with age, two recent cross-sectional studies found that bone loss continued into the ninth decade of life. The Framingham study identified a linear decline in bone mass in the proximal femur and proximal radius, but not the ultradistal radius (5). Annual changes in bone mineral density were approximately −0.53% for the trochanter, −0.68% for the femoral neck, and −0.88% for the proximal radius, but only −0.16% for the ultradistal radius. This pattern of loss continued through the late 70s and 80s and into the mid-90s. Steiger et al. found that declines in the lumbar spine bone density were considerably less than the hip or radial losses (6). Bone density declined 16% in the spine, 18%–20% in the radius, and 26% in the femoral neck between 65 and 85 years of age. A linear relationship between bone loss and age was again identified into the mid-80s. Since bone loss continues into the ninth decade, the effect of late postmenopausal bone loss can be devastating.

Many clinicians assume that osteoporosis in the elderly is untreatable and that future frac-

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tures are inevitable. This nihilistic approach is not justified. Although the bone density of most elderly women decreases below the theoretical fracture threshold, the inverse relationship between bone mineral density and fractures continues below the fracture threshold; that is, the higher the bone density, the lower the fracture risk (1, 3). The fracture threshold does not represent an all-or-nothing phenomenon. For example, clinicians would consider a patient with a blood pressure of 210/110 mm Hg and a patient with a blood pressure of 165/95 mm Hg as hypertensive, and even a 10% decrease in blood pressure would be considered beneficial to both patients, although the first patient would remain hypertensive. Similarly, individuals below the theoretical fracture threshold may, in fact, receive significant benefit from a slight decrease in their risk of fracture through preventing further bone loss or providing a small increase in bone mass from active treatment.

Bone histomorphometry in the aged has shown both increased and decreased bone turnover in different individuals. A decrease in the connectivity of trabecular plates has been noted. Furthermore, new bone formation declines with decreased repair of microfractures, increasing the risk of fracture (7).

Risk Factors for Fracture in The Elderly

Bone density clearly decreases with age. In fact, virtually all older women are below the theoretical fracture threshold and are at increased risk for fracture. Nonetheless, continued bone density loss only increases the already high risk for fracture. Numerous studies have shown increased risk of fracture with each incremental decline in bone mineral density (1, 3). Paganini-Hill et al. identified multiple risk factors for hip fracture, including the presence of diabetes, thinness, tallness, cigarette smoking, alcohol intake, inactivity, early menopause, and decreased sunlight exposure, many of which are clearly associated with decreased bone mineral density (8).

The elderly are also at increased risk of falling. One-third of persons over 65 fall each year; however, only 6% of these falls lead to fractures. The increased fall risk in the elderly may be related to comorbid illnesses, polypharmacy, or other concomitants of aging, such as postural hypotension, Parkinson's disease, stroke, or lower extremity disability such as arthritis. Visual loss from cataracts, glaucoma, or macular degeneration also places elderly individuals at risk for falls. Medications that increase fall risk include antihypertensive drugs, sedatives, antipsychotic agents, and tricyclic antidepressants (9).

Therapy of the Older Osteoporotic Woman

There is now definitive proof of beneficial treatment in elderly women with osteoporosis; therefore, each individual patient should be evaluated for therapy that may provide the most benefit and acceptable risk. An individual with low bone density alone may be treated less aggressively than a patient who has experienced multiple vertebral fractures. Three modalities of treatment for osteoporosis are discussed below: calcium, vitamin D, and antiresorptive agents such as estrogen.

Calcium. Calcium deficiency is common as women age, because of both poor gastrointestinal absorption and low calcium intake. Absorption of calcium from the intestine decreases 20%–25% between ages 40 and 60 owing to the combined effects of loss of estrogen at menopause and aging (10). In the 1980 NHANES survey, the median daily intake of calcium among women older than 44 years was 475 mg, less than half the recommended calcium intake for postmenopausal women (11). The roles of low-calcium diets and poor calcium absorption in the elderly osteoporotic are not well understood, but there is some evidence that a relative calcium insufficiency may stimulate bone resorption by increasing levels of parathyroid hormone (12).

Recent studies have confirmed earlier findings that calcium stabilizes bone loss more effectively in late postmenopausal women than in early menopausal women. A study by Dawson-Hughes et al. showed calcium supplementation with 500 mg of calcium citrate malate stabilized spinal bone loss and actually increased bone density in the radius and femoral neck among late menopausal women with a dietary calcium intake of 400 mg or less (13). Reid et al. recently showed a beneficial effect of 1000 mg of calcium supplementation among women 10 years past menopause who had a relatively high baseline dietary intake of calcium of 750 mg (14). The rate of bone loss was decreased at the hip, and bone density actually increased in the lumbar spine. A 14-year prospective study found that a dietary calcium intake greater than 765 mg/day was associated with a 60% reduction in hip fracture risk (15). Although no fracture data showing benefit from calcium supplementation alone are available, a recent study of 3,270 elderly French women living in nursing homes showed fewer nonvertebral fractures among women randomly assigned to receive 1,200 mg of calcium and 800 IU of vitamin D than among those receiving placebo. Women receiving the combination of calcium and vitamin D experienced 27% fewer hip fractures and 26% fewer nonvertebral fractures than women on placebo (16).

The metabolic effects of six months of calcium supplementation include significant declines in both serum parathyroid levels and 1,25-OH vitamin D levels (17). Bone turnover parameters, including serum bone Gla protein and urinary hydroxyproline excretion levels, did not change. The mechanism of action for calcium supplementation in late postmenopausal women may be related to suppression of age-related increases in parathyroid hormone levels that might increase bone resorption.

Finally, Orwoll et al. conducted a histomorphometric study of the effects of 1,200 mg of calcium carbonate on bone in elderly osteoporotic women with an average dietary calcium intake of 854 mg (7). The baseline bone biopsy revealed depressed bone remodeling rates without evidence of osteomalacia. Repeat bone biopsies showed an unexpected decrease in both mineralization lag time and the duration of remodeling cycles, suggesting that a relative calcium deficiency in late postmenopausal osteoporosis may impair the mineralization phase of remodeling.

In summary, recent data suggest that calcium supplementation with 500–1,000 mg/day stabilizes both trabecular and cortical bone loss in women during the late postmenopausal years. This effect appears to be most powerful in women with low dietary calcium intakes of less than 400 mg/day, but it remains beneficial for women with higher dietary calcium intakes.

Achlorhydria, cost, and compliance complicate calcium supplementation in the elderly. Achlorhydria increases considerably with age, decreasing the level of free acid in the unfed stomach; one study showed that almost 40% of women over age 50 have no free acid in the unfed state (18). Calcium carbonate is not absorbed well without gastric acid secretion and, therefore, should not be given on an empty stomach to elderly patients. Absorption studies have found that calcium citrate is better absorbed through the gastrointestinal tract than calcium carbonate, especially when taken without food (19). Absorption of calcium from the gastrointestinal tract is also dose dependent, with minimal increases in calcium absorption in doses greater than 500 mg (19).

Calcium carbonate remains the least expensive, most widely available source of calcium supplementation, which must be considered when prescribing to the elderly patient. If preferred for these reasons, calcium carbonate should be given with meals, and all calcium supplements should be prescribed in divided doses if the patient is taking more than 500 mg of calcium.

Compliance with calcium supplements is related to their side effects, especially constipation in the elderly. Starting with low doses of calcium supplementation and building up to the desired dose may be helpful; however, many elderly patients will need to change from calcium carbonate to a less constipating source of calcium, such as calcium citrate, calcium citrate malate, or a liquid form, calcium glubionate. Unfortunately, calcium citrate malate has been commercially available only in fortified fruit juices (20).

The overall required dose of calcium supplementation varies with the patient's dietary calcium intake. Although recent studies suggest a total intake of 800 mg may be sufficient, a more conservative guideline of approximately 1,200 mg of total calcium intake may compensate for individual variation in absorption. This total intake of calcium is unlikely to cause clinical problems unless the patient is hypercalcemic or hypercalciuric. Hypercalciuria may be suggested by a personal or family history of kidney stones or an unexpectedly low bone density (more than 2 SD below normal for age), which may be due to renal calcium wasting.

Vitamin D. Vitamin D insufficiency has been well described in the elderly population. McKenna suggests that 25% of community-dwelling elderly people have low vitamin D values in the winter (21). Estimates of vitamin D intake by community-dwelling older people is approximately 100 IU per day—half the recommended daily allowance, and one-quarter of the dose available in most multivitamins (11). A recent study of 22 homebound elderly patients aged 68–96 found one-third had serum levels of vitamin D less than 25 mmol/L, despite a dietary intake of 467 IU daily (22). These authors suggest that 400 IU of dietary intake is not sufficient in homebound elderly patients without sun exposure. In addition to decreased oral intake of vitamin D in the elderly, aging appears to decrease skin and renal production of vitamin D.

Vitamin D insufficiency can affect bone loss in the elderly in at least two ways: by decreasing calcium absorption and by leading to osteomalacia. Osteomalacia is a bone disorder caused by vitamin D deficiency where normal bone matrix is formed but is not mineralized. The prevalence of low-grade osteomalacia among patients with intracapsular hip fracture in the United States was reported as 25% in 32 patients studied by Sokoloff (23). Furthermore, 40% of 172 patients hospitalized with hip fracture had low 25-OH vitamin D levels, reflecting decreased vitamin D intake (24). Vitamin D insufficiency also increases secretion of parathyroid hormone, which in turn increases resorption of bone (11). Dawson-Hughes et al. randomized 249 postmenopausal women with usual daily vitamin D intakes of 100 IU to receive either 400 IU of vitamin D or placebo, in addition to 377 mg/day of calcium (25). Women taking vitamin D decreased their wintertime spinal bone loss significantly (-0.54%, instead of -1.22% taking placebo). There was a significant one-year increase in bone density of 0.88% in the group taking vitamin D and calcium, compared to an increase of 0.15% in those taking calcium and placebo.

The French nursing home study of over 3,000 ambulatory women randomized to receive either 1.2 g of calcium and 800 IU of vitamin D or placebo found over a 25% decline in both hip and nonvertebral fractures in the treatment group. At baseline, this population had low serum vitamin D values and slightly elevated parathyroid hormone values, which normalized in the group on calcium and vitamin D supplementation (16).

Overall, these studies support the recommendation that elderly individuals supplement their low dietary intake of vitamin D with 400 IU of vitamin D available in a multivitamin. Homebound elderly persons deprived of sun exposure should increase their vitamin D intake to 800 IU/day.

The data on pharmacologic doses of vitamin D or calcitriol (1,25-OH2 vitamin D) in the treatment of osteoporosis are contradictory. Some studies found higher fracture rates or greater loss of bone density on calcitriol, but others showed decreased bone loss or decreased fractures (26–30). The most recent study utilizing low doses of calcitriol (0.25 μg twice a day) found markedly fewer vertebral fractures among women receiving calcitriol for three years than among women receiving calcium alone (28). Elevations of serum calcium or creatinine were infrequent in the low doses used in this study; however, increased serum and urinary calcium levels were identified in previous studies (29, 30). Thus, patients treated with calcitriol must calcium-restrict their diets to avoid symptomatic hypercalcemia. At present, calcitriol is not indicated for the treatment of primary osteoporosis outside of a research setting.

Antiresorptive Therapy in the Elderly. Estrogen replacement therapy (ERT) remains the treatment of choice in the prevention of osteoporosis and in the treatment of women with osteoporosis under age 70. If estrogen replacement therapy is continued, its efficacy is sustained at least until age 70. However, it is not clear that newly prescribing ERT to older women will be beneficial. Most studies of ERT have focused on women younger than 65.

Two randomized clinical trials including women over 65 showed a significant increase in bone density for women receiving estrogen. One trial of 39 women showed a significant decrease in vertebral fracture rates in the group receiving transdermal estrogen; however, few women over age 70 were included in this study (31). A population-based cohort study in Sweden found that women who had ever used estrogen had a lower relative risk for hip fracture of 0.79 (0.68–0.93) (32). However, patients older than 60 had no significant decrease in hip fracture, whether they had ever used estrogen in the past or had recently used estrogens in the last five years. A recent case-control study found a protective effect for women taking estrogen, the relative risk for hip fracture being 0.55 (0.31–0.85) (33). Estrogen appeared to be less effective for women over age 80.

Use of ERT in women over 70 years of age must be based on studies in younger women. Therefore, when prescribing hormone replacement therapy, it is essential to assess individual risks for fracture, cardiovascular disease, and breast cancer. A recent meta-analysis of hormone replacement therapy suggests an overall benefit with increased life expectancy for women at high risk of hip fracture (1.1 years) or heart disease (1.6 years) (34). Women at high risk for breast cancer may increase their lifetime probability of breast cancer as a result of ERT.

Although studies of estrogen and cardiovascular disease have shown benefit from estrogen replacement therapy, including a decreased relative risk in both coronary artery disease and mortality, benefit from ERT for women over 70 has not been consistently shown. For example, the ten-year prospective observational study of nurses 30–63 years old at entry found a relative risk of mortality of 0.56 among current estrogen users. The relative risk in the oldest age group, however, suggested a trend toward current use increasing relative risk of mortality to 1.35 (not significant) (35). Other studies following patients into their 70s showed decreases in age-adjusted mortality rates. The Framingham study found a protective effect for younger women, but, again, a nonsignificant adverse effect was observed in older women (36).

Although controversy exists over the role of ERT in breast cancer, a recent meta-analysis suggests a 30% increase in risk after 15 years of ERT (37). Estrogen replacement therapy should only be considered for women willing and able to undergo appropriate gynecologic follow-up, regular breast examination, and mammography.

Calcitonin. Calcitonin, a hormone derived from the thyroid gland, has been shown to decrease bone loss, but no prospective data are available to show a protective effect against fractures. A recent case-control study of 2,086 women with hip fractures and 3,532 age-matched controls found a protective effect for women taking calcitonin and calcium with a relative risk of hip fractures of 0.63 (confidence interval, 0.44–0.90) (33). The relative risk was 0.82 (0.63–1.07) for calcium alone and 0.78 (0.48–1.27) for calcitonin alone.

Calcitonin acts as an analgesic for some patients with acute compression fractures, although many patients do not tolerate the side effects of nausea and flushing or refuse parenteral administration. Furthermore, calcitonin therapy is very expensive; moreover, antibodies to the hormone frequently develop after several years of use. Calcitonin in the form of a nasal spray is widely utilized throughout the European continent. This preparation of the agent is better tolerated than parenteral injection, yet the drug remains very expensive, and its efficacy in fracture prevention is not clearly demonstrated.

Bisphosphonates. Bisphosphonates, new medications for osteoporosis, are undergoing extensive clinical trials for use in both the treatment and prevention of osteoporosis. Bisphosphonates act by inhibiting resorption of bone by the osteoclast. Etidronate, a bisphosphonate approved for treatment of Paget's disease, decreased bone loss and vertebral fractures in two small studies of osteoporotic women (38, 39). Unfortunately, the two studies of the effects of etidronate on vertebral compression fractures were complicated by either unusually high or low fracture rates in the control groups, obfuscating evaluation of treatment effect.

Several clinical trials are now under way in this country evaluating the effect of newer bisphosphonate medications on bone loss and prevention of vertebral fractures. Initial studies in Europe have shown that some of the experimental bisphosphonates prevent postmenopausal bone loss (40).

Thiazide Diuretics. Thiazide diuretics decrease urinary calcium excretion and may decrease the risk of osteoporotic fractures by improving net calcium balance. Seven of eight studies reviewed suggest protection from hip fracture, higher bone density, or slower bone loss in thiazide users (41–48). No randomized clinical trials of thiazides for osteoporosis have been undertaken.

Who to Treat

No guidelines have been established for the treatment of osteoporosis in elderly women. Recent studies suggest that most elderly women should receive appropriate calcium supplementation to approximate a daily intake of 1,000–1,200 mg of calcium. Most individuals should also receive 400 IU of vitamin D, especially during the winter months in northern latitudes. Increased doses of vitamin D should be considered for the institutionalized elderly and for individuals with malnutrition, malabsorption, or evidence of osteomalacia.

Since most women fall below the fracture threshold as they age, studies to determine secondary causes of osteoporosis are recommended for those who have lower bone density than expected for their age, a rapid succession of fractures, or other clues that postmenopausal osteoporosis is not the sole perpetrator of thin bones. As examples, a rapid succession of vertebral fractures may be due to multiple myeloma, elevated serum calcium levels may be due to hyperparathyroidism, and a family history of kidney stones may suggest renal hypercalciuria.

Studies for secondary causes must be tailored to the individual patient, but might include an immunoprotein electrophoresis, 24-hr urine test for calcium, creatinine, Bence Jones proteins or free cortisol, 25-hydroxy vitamin D levels, sensitive thyroid-stimulating hormone, parameters of malabsorption such as carotene, iron, or vitamin B_{12} levels, or parathyroid hormone measures. In elderly patients, a measure of intact parathyroid hormone may be more accurate than the midmolecule assay, especially when renal insufficiency is present.

If a secondary cause of bone loss is present, appropriate therapy should be instituted, such as thiazide diuretics when the patient has renal hypercalciuria.

If patients have lower than expected bone density or begin fracturing, antiresorptive therapy should be considered. Antiresorptive agents are most effective in high bone turnover disease.

Measures of bone turnover, such as osteocalcin or pyridinoline crosslinks, may help in deciding whom to treat. The choice of antiresorptive agent remains a complex decision in light of the lack of data in the elderly. The cardiovascular benefits of estrogen may not be evident over age 70, the injection of calcitonin may be difficult because of visual changes, arthritis, or compliance with injections, and the gastrointestinal side effects and poor absorption of bisphosphonates may limit their acceptability. Once again, choice of therapy must be tailored to each individual to maximize compliance and safety and reduce bone loss.

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The Principle of Autonomy and the Older Patient

Diane E. Meier, M.D.

The rising interest in the ethical aspects of modern medical practice results from two recent and historically unprecedented phenomena: the growth in numbers of dependent elderly persons, and the dizzying velocity of advances in medical technology that have occurred over the last several decades. The dramatic 28-year gain in life expectancy over the first 50 years of the twentieth century is equivalent to that gained in the 4,000 years preceding this century, from the Bronze Age (2000 BC) to the year 1900.

There are several reasons for this remarkable increase in length of life, and they are simpler than one might guess; the extension of the life span is primarily due to better public and preventive health measures, such as clean water, basic nutrition, public sanitation measures, and routine prenatal care. This improvement in life expectancy predated the advent of antibiotics and the high technologic diagnostic and therapeutic procedures that are currently breaking our health care budget. The recent resurgence of tuberculosis despite the availability of effective drug treatment is eloquent testimony to the primary contribution of social and public health factors, primarily poverty, on the incidence of disease.

As a consequence of this recent gain in life expectancy, the numbers of older adults in the United States have reached new highs: 12% of the population is now 65 years old or older, a percentage predicted to increase to 22% by the year 2040. One often-quoted statistic is that the fastest-growing segment of the population is the group of persons over age 85 (1). The impact of this growth in number of older adults will be felt throughout society, but nowhere more powerfully than on the practice of medicine.

The second factor behind rising interest in medical ethics is the influence of the so-called technology imperative on the modern practice of medicine, whereby the existence of a technology with any possibility of benefit, no matter how remote, seems to mandate its use (2). In the early years of this century, medical decisions for ill and elderly persons were greatly simplified by the physician's inability to substantially alter the course of diseases (usually infectious and quick) leading to death. Because little power to affect the ultimate course of illness was available to either doctors or patients, conflict over decisional authority and appropriate applications of technology did not exist.

Changes in these aspects of medical practice have resulted from exponential technical advances in ability to prolong life despite chronic irreversible illnesses, such as end-stage lung, heart, and kidney disorders, and debilitating neurologic degenerative diseases, such as stroke and Alzheimer's disease. This very recent shift, from death and dying as an unchangeable and usually short-term process to a state of life amenable to multiple interventions and prolongation over a long period of time, has fueled interest in the study of medical ethics and an attempt to apply ethical principles to medical care and medical decisions for persons approaching the end of their lives.

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Autonomy and Frail Elderly Patients

In part because of the increasing power of medicine to prolong life and the uncertain benefit of such a technologic imperative for some older adults, a growing movement for patients' self-determination, based on the ethical principle of individual self-determination, has begun to have a major influence on health-care policy. The informing value of this patients' rights movement is the principle of autonomy that embodies respect for persons and their free choice. Well grounded in the legal precedent of this country, it was best expressed by Justice Benjamin Cardozo in a 1914 decision: "Every human being of adult years and sound mind has a right to determine what shall be done with his own body" (3). Recent court decisions, such as the Quinlan and Cruzan cases, have also consistently upheld the primacy of individual free will in medical decision making, particularly in considerations of termination of life support (4, 5).

This concern for the promotion of patient autonomy in medical decision making has also found expression in advance directives and living wills, whereby people can state their wishes regarding those life-sustaining treatments that they may or may not wish to have applied to them at the end of their life. Similarly, the recent availability of proxy appointments, by which people of intact mental capacity may appoint another individual to make medical decisions on their behalf in case of any future mental incapacity, is another method of trying to advance autonomy in health-care decisions. These efforts have made their way into law in the form of the 1991 federal Patient Self-Determination Act, which requires that all institutions receiving Medicare or Medicaid reimbursement provide adult patients, on admission, with written information on advance directives and on the right of adults to refuse any life-sustaining treatments (6). In New York State, and in many other states as well, the law permits patients to appoint proxies for health-care decisions in case any future mental incapacity develops (7). These laws were enacted to enhance the power of individuals if and when they find themselves literally at the mercy of modern medicine; the laws are an attempt at maximizing the chances that any treatments employed are truly in accord with the patient's values and preferences.

This seems all to the good. But the application of these strict autonomy-based principles to medical decisions in frail older persons is fraught with contradiction and ambiguity. Many features of being an older adult necessarily restrict the unfettered primacy of patient self-determination: the progressive series of personal and functional losses that tend to accompany aging; the often unconscious ageism of a society that places great emphasis on rugged self-reliance and independence, characteristics that are often lost in older adults because of the burdens of chronic illnesses and associated disability that eventually afflict most of us if we are fortunate enough to reach old age; the associated consequence of increasing dependency on other people for daily living, a reality that is often profoundly distressing both to older adults and to their families and that may make true autonomous decision making nearly impossible; and finally, the spiritual and emotional recognition of the relative imminence of death that accompanies this stage of human development. These aspects of being old often create a special vulnerability in the older patient that requires appropriate sensitivity and awareness on the part of the physician and that prohibits a facile reliance on patient autonomy as a basis for medical decision making.

Problems in Applying The Principle of Autonomy to Frail Patients

What are the drawbacks to utilizing advance directives and proxy appointments to maximize the medical autonomy of persons with diminished capacity?

- First, and not surprisingly, many patients do not want to dwell in detail on the prospect of their future incompetence and death and, therefore, do not wish to discuss advance directives (8).
- Second, even when a patient completes a living-will type of advance directive, the forms are often so vague and so open to interpretation that they are of little guidance when specific treatment decisions are required.
- Third, a preference expressed during good health and relatively high levels of function may not persist; that is, people can change their minds, and in the real world of clinical medicine, often do, depending on changing circumstances (8, 9). This problem points to the obvious advantage of a proxy being appointed to work with the doctor in "real time" as circumstances unfold.
- Finally, in some cases of chronic dementia, patients may seem to have a pleasant and enjoyable quality of life that would ordinarily deserve continued medical treatment, but their

> advance directive refuses life-sustaining treatment under such circumstances (9). Should the doctor treat this patient, or should she instead have primary loyalty to the document executed by a younger version of this person under quite different circumstances?

Similar problems plague the proxy appointment process: proxies may be unable to distinguish their own best interests from the patient's wishes or best interests; many studies have demonstrated fairly poor concordance of proxy choices with the patient's stated preferences (10, 11); and proxies may act in direct opposition to the patient's treatment directive.

Changes Needed To Promote Autonomy

To ensure that these well-intentioned efforts to promote patient self-determination actually result in decisions that most people would judge to be in their best interest, several changes are needed:

1. Advance treatment directives should stimulate discussion between doctor and patient, rather than replace it. Obviously, such discussions should occur when the patient is in a stable condition and not when a patient is being admitted to a hospital for an acute illness.
2. Intensive public and professional education on the advantages and limitations of modern medical technology is required to modify both patients' and doctors' unrealistic expectations and hopes.
3. Care must be taken to avoid coercing patients to complete treatment directives in order to conserve scarce health care dollars—we must not ask patients and families and their personal physicians to ration care in the guise of promoting their control over medical decisions at the end of life—that responsibility should rest with democratically legislated limits on spending and equitably applied medical prognostic criteria for the use of life-sustaining technologies.
4. Despite our best efforts, the principle of autonomy is often nearly irrelevant to medical decision making for frail older persons at the end of life. As clinicians, we must develop flexibility to rely on autonomous choices when that is a meaningful concept for the patient at hand, and to return to more traditional best-interest criteria when it is not.

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Education, Clinical Services, and Research On Treating Older People

Long-Term Care

A Teaching Nursing Home:

Ten Years of Partnership between the Jewish Home and Hospital for Aged and the Mount Sinai School of Medicine

Leslie S. Libow, M.D.

QUALITY in long-term care depends on a linkage to education. Thus, there is no true quality nursing home without an academic component and there is no true geriatric medicine without a nursing home program at its center (1).

America's first teaching nursing homes emphasized training of medical students, residents, and fellows, combined with program innovation and research. These academic nursing homes, as they were referred to in the start-up years of 1967 to 1977, provided the base for the development of U.S.-trained geriatricians and for the development of the field of geriatric medicine (1–5). Great impetus was given to this movement by the far-reaching paper "The Teaching Nursing Home" (6).

The more recent experience of the Jewish Home and Hospital for Aged (JHHA) of New York and the Mount Sinai School of Medicine in developing a teaching nursing home partnership began in 1982 (7). The program has encompassed more than 1,000 senior medical students in an obligatory clerkship and 50 fellows who have completed their training at the nursing home. Our programs have led to new clinical approaches and teaching curricula and to research into a variety of issues important to long-term care. Interest has been strong among participating medical students, graduate physicians, staff, and patients and their families, as well as among the Board of Trustees and administration (5, 8, 9).

Many teaching nursing homes have documented their experience (9–15) though few, if any, have described a clerkship with an obligatory rotation of all medical students.

The goals have been to train every medical student in the art and science of geriatric medicine while improving care for the frail elderly. We at the nursing home have been mentoring the fellows in their growth as clinicians, teachers, and researchers, while at the same time developing strong communication with the administrative leadership and the Board of Trustees of The Jewish Home and Hospital for Aged and The Mount Sinai Medical Center.

Education

Geriatrics as a Clinical Specialty. Geriatrics is partly defined by the phases and places where its approaches are needed and expressed. Thus, it is chronic illnesses, functional disabilities, the prevention of secondary and tertiary complications that are the focus of geriatrics. Similarly, it is at the nursing home and the ambulatory clinic and in home care that the greatest need exists for input from geriatric medicine.

Of course, the hospital too needs innovation with regard to its care of the acutely ill frail older patients. There are some who believe that geriatrics is not a clinical-practice specialty, but more akin to clinical pharmacology or infectious disease. They see geriatrics as an institutional-based addition to the current practice of medicine. That view is too restrictive and fails to encompass the major clinical responsibilities that define the shape and substance of the field of geriatrics.

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Components of the Geriatrics Curriculum in Nursing Home Medicine. Because of the key role of long-term care in geriatrics, and because of the willingness of the nursing home and its home-care program to participate as training sites, we at The Jewish Home and Hospital and the Mount Sinai School of Medicine obliged all senior-year medical students to rotate to the nursing home and its multitude of institutional and community programs. The typical components of the two-week and four-week curriculum, which highlights multiplicity of problems, is as follows:

- Functional assessment and intervention: physical and mental
- Ethical dilemmas, ethics rounds, and other approaches
- Rehabilitation; diagnosis and treatment
- Home care—visits and teams
- Body of knowledge of long-term care
  - Pneumonia: organism; treatments; vaccine efficacy
  - Epidemics: flu; diarrhea
  - Patterns of medication use
  - Difficult diagnosis of the common problem
- Mentors for research projects
- Daily rounds in a variety of disciplines
- Screening and prevention

Although all students were in their senior year in medical school, most students confronted several first-time experiences in this rotation, including (a) the first house call and home-care team experience, revealing the power of this nonhospital approach, and the key role of clinicians other than physicians (16); (b) the first opportunity to learn the skills of rehabilitation medicine and of diagnosing and prescribing for physical disabilities such as hemiplegia, fractured hip, and unsteady gait (17); (c) the first obligatory clerkship in which the major educational experience was not at the acute-care hospital but rather at long-term care settings (8, 18, 19).

Attitudes of Rotation Graduates. In 1983, before the arrival of the first senior class obligated to undergo the nursing home rotation, a delegation of students came to see program organizers and protested the new curriculum. It was bad enough, they said, to have the nation's first, or one of the first, obligatory four-week geriatric clerkships, but to spend two to four of those weeks on the nursing home programs was unacceptable. We clarified their duties, pointed out the unique experiences available, and did not change the curriculum (7, 18, 19).

More than 10 years and 1,000 students later, those predictable complaints have receded. Student evaluations place this now established geriatrics curriculum alongside the classic clerkships in medicine, surgery, and pediatrics.

JHHA researchers located and mailed questionnaires to 600 of the 1,000 graduates and received 306 anonymously completed questionnaires. Approximately 70% of these clinicians and former JHHA students favor keeping the four-week geriatrics curriculum or increasing it to more time whereas 30% favor decreasing the clerkship time (Olson E, Libow LS, Chichin E, "Long-term effects of a mandatory fourth-year medical student rotation in geriatric medicine," unpublished research):

• Would recommend increasing length of geriatric clerkship	20.9%
• Think length of clerkship should remain the same	48.6%
• Would recommend decreasing length of geriatric clerkship	30.5%

This strong support derives from the value of training in treating older patients as seen by clinicians once they are in residency, fellowship, or practice.

Research

The teaching nursing home academic staff, with central input from fellows, chose six research areas—education; rehabilitation, falls, and restraints; urinary incontinence; infection and immunology; ethical dilemmas; and Alzheimer's disease and other dementias—as focal in improving the quality of life of patients in long-term care. The interests of particular fellows has led the mentor-fellow partnerships into new areas of research beyond these six.

Among the many studies completed are these:

Education. Experiences of students have been measured and show a statistically significant increase in knowledge in comparisons of before-clerkship and after-clerkship knowledge levels (18, 19). The positive view of graduates has been described above.

Rehabilitation. Published reports have described a falls consultation service (20) and a rehabilitation unit (17) in the nursing home. More recently, data have been gathered delineating a decrease in use of restraints from 51% to 3% at JHHA, and a similar trend in a national restraint reduction effort which we have created in collaboration with The Commonwealth Fund and Rensselaer Polytechnic Institute (21).

Urinary Incontinence. Fellows are trained in urodynamics and the assessment of incontinence. Our studies have shown the remarkably high prevalence of urinary incontinence and its surprising etiology (detrusor hyper-reflexia) in most elderly diabetics (22–24).

Infection and Immunology. Jewish Home and Hospital for Aged studies have shown the efficacy of the influenza vaccine in decreasing respiratory infection and mortality in the nursing home population (25). In addition, the high rate of occurrence of anergy in the frail elderly has been clarified, and its mechanism is under study.

Ethical Dilemmas. A variety of clinical ethical issues have been studied. One example is the discordance between patients' wishes and their caregivers' beliefs about their wishes (26). In addition, an ethics rounds (27) and a center on ethics in long-term care (28) have been created.

Alzheimer's Disease and Other Dementias. Alzheimer's disease is being studied in collaboration with investigators and laboratories at The Mount Sinai Medical Center. JHHA is unusual as a long-term care center in having on-site autopsies. The Alzheimer's disease research focus is on correlating clinical cognitive changes with anatomic and biochemical changes. We are also studying the relationship of Alzheimer's disease to changes in the normal aging brain.

Obstacles and Challenges

In 1982 the curriculum committee of Mount Sinai School of Medicine was reluctant to cooperate with the Dean's commitment to the four-week clerkship in geriatric medicine. Thus, resistance existed even in the face of the dedicated plan to create this innovation. This expected response was surmounted. It was our decision to heavily utilize long-term care as a basis for education. Over the ensuing years the hospital component of the geriatric curriculum developed strongly too.

The nursing home staff had the anticipated discomfort and distrust of the medical school and hospital faculty. Our approach was to assign medical school faculty members to primary teaching, clinical, and administrative responsibilities at the nursing home, so that they would not be outsiders. This has produced a collegial working relationship, the needs of the nursing home always remaining primary while faculty identification with the nursing home patients and programs is strong.

Overt discomfort at the nursing home by some faculty in the geriatrics department was a bit surprising. We ultimately identified as JHHA faculty those individuals comfortable with and committed to long-term care.

Geriatric medical programs at the nursing home attract philanthropic and government support. The combined efforts of the JHHA and the Mount Sinai School of Medicine established an endowed professorship in long-term care (the Greenwall Professorship). JHHA established an Ethics Center in Long Term Care (Schimper, Greenberg & Zicklin Foundation); a national Restraint Reduction Project (Commonwealth Fund), and a rehabilitation program (the Brookdale Foundation and Federation of Jewish Philanthropies). In addition, since 1987 government funds have paid for a sizable portion of the fellowship salaries.

Summary and Conclusions

The JHHA is moving forward into new areas of pursuit within long-term care, including studies of the pneumonia vaccine; the cause of Alzheimer's disease; the difference between the brain of the Alzheimer's patient and the normal aging brain; new patterns and approaches in pharmacy and pharmacology; and the new nursing home of the 21st century in a changing health care environment.

Students and graduate physicians will continue to strengthen their clinical identity by virtue of this exposure, and those of all ages will benefit from the research and advances in patient care coming out of this program.

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Ethical Issues in the Nursing Home

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Abstract

The nursing home is the site of many ethical dilemmas. The majority of these are linked to the high prevalence of dementia and other disorders that affect decisional capacity, thus dictating the need for surrogate decision-making. Even when nursing home residents have utilized advance directives to guide their future care, many issues remain in the decision-making process. This article explores the challenges of medical decision-making for a frail elderly population.

A PRIMARY FOCUS of ethical discussion in the nursing home is the nursing home resident without capacity. Historically, the family and the primary care physician were the decision-makers for this group of individuals. Although some states continue to recognize this approach and have adopted legislation to support it, the majority of states—including New York—do not currently do so.

The Legal Climate. Major court decisions over the past several years have, in fact, supported a trend away from family decision-making to a decision-making standard that is resident-focused and stresses the importance of advance directives (living wills and proxy designations) and "substituted judgement" decisions by surrogate decision-makers. In other words, surrogate decisions should, to the extent possible, mirror the decisions the patients themselves would make if they were capable of doing so.

This trend culminated in 1990 in the Cruzan decision, in which the Supreme Court of the United States reaffirmed patient autonomy and the right to refuse treatment. However, at the same time, it rendered families powerless to speak for their incapacitated family members in states that required clear-cut directives from the patients prior to their incapacity (1). The Appellate Court of New York State had reached a similar decision in 1988 in the O'Connor case, in which the precedent of a standard of "clear and convincing" evidence was adopted before life-sustaining treatments could be removed from patients incapacitated in decision-making (2). Unfortunately, this standard is difficult to meet without written directives.

In response to the Cruzan decision, a proxy law went into effect in New York State in 1991, allowing people with capacity to appoint a decision-maker in the event of incapacity. The passage by Congress in 1990 of the Patient Self-Determination Act encouraged states to adopt legislation that allows the use of advance directives for health care. However, this still left open the question of decision-making for residents who lacked capacity and had never made use of an advance directive. Equally important, it did not address who should make treatment decisions for this vulnerable group of individuals.

In an attempt to deal with this issue, the New York State Task Force on Life and the Law has proposed legislation to address surrogate decision-making for patients without capacity. However, the proposal is in the early stages of the legislative process, and how long it will be before the legislation becomes reality is not clear. Meanwhile, making life-sustaining treatment decisions for residents without capacity in New York State and in other states in which such laws do

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not exist is extremely difficult. In these states, such decisions can only be made when adequate advance directives are in place prior to the loss of capacity or where other forms of "clear and convincing" evidence exist.

This reliance on advance directives means that their strengths and weaknesses affect many of the ethical issues faced in the nursing home setting, as well as other situations in which clinicians turn to these documents. Even when requests to limit treatment for people without capacity are supported by valid directives, much work remains before any conclusion can be reached and a plan of treatment or nontreatment implemented. This situation also holds, however, when requests are made to limit treatment by a person with decision-making capacity.

Treatment Decision-Making: The Process

Medical Evaluation. How does one approach difficult treatment decisions in the nursing home? At the heart of every discussion to limit treatment is the need for a sound and thorough medical evaluation. Some older people may wish to forgo life-sustaining treatments just because they are experiencing pain or discomfort or profound functional losses resulting from acute or chronic illnesses. The often confusing presentation of disease in the elderly in general, combined with the tendency to overlook illness in the elderly because it is attributed to "old age," may lead to some people being considered "terminally or irreversibly ill" when they really have a reversible medical problem whose cure could change their whole outlook on continued life.

Advance directives invoked for incompetent residents are often linked to stated conditions, such as "terminally ill" or "irreversible mental impairment." The determination must be made objectively to insure that the person indeed meets the conditions of the directive. Clinicians are often too quick to draw conclusions in either direction. On the one hand, they may deem the situation hopeless when it is not. On the other hand, they may disagree with residents or families over the futility of the situation. Again, achieving this comprehensive and objective review of a resident's actual medical status is really the first challenge in these cases. And, unfortunately, this can often be complicated by clinicians' ambivalence toward refusal of treatment.

Determining Capacity. The next major challenge faced in the nursing home is the determination of decision-making capacity or competence. A resident must be deemed competent to refuse treatment, and in the case of proxy decisions, a resident must be deemed incompetent or incapable of participating in the decision process before the assigned agent can speak for him or her.

One cannot talk about capacity or competence without first talking about informed consent. The criteria for informed consent are: (a) it must be voluntary; (b) it must be given by a person who is competent—the person must have the mental capacity to make and communicate autonomous decisions; and (c) it must be informed—patients must be informed of all their options and the risks and benefits of each, and they must appear to understand the information (3).

The questions to be asked in assessing competency or capacity include whether the person can make and communicate (by spoken word or otherwise) decisions regarding his or her own life, can offer any rational reasons for the decision, and understands the likely risks and benefits of the options presented and that those risks and benefits apply to him or her (4).

In the nursing home, we most often run into situations of partial competence. The rule of thumb is that the degree of competence or capacity needed is directly related to the gravity of the decision. When a sick person is refusing life-sustaining therapies, the level of competence or capacity should be quite high, but need not be what is considered normal. Studies have shown that even when older people do not do as well as younger people in understanding and recalling information (for example, the information describing a procedure for which consent is needed), they still make reasonable decisions that reflect their ability to use the information they do process to assess benefits and risks (5).

Influence of Depression. Another factor that may complicate the determination of capacity in the nursing home is the presence of depression. As much as 24% of nursing home residents may suffer from depression (6). Although depression has not been found to affect overall comprehension and the ability to give informed consent (7), many believe it influences, at least to some degree, a person's decision on the use of life-sustaining treatment.

Many elderly people in nursing homes suffer from severely disabling conditions that entail loss of function and independence and little to no hope of recovery, and these patients may have a concomitant depression. It has been argued that aggressive treatment should be instituted for depression in elderly patients, especially those who are medically ill, because depressive disorders are often associated with an increased mortality rate in such patients. However, this should not be considered the only acceptable option (8).

Lee has also argued that although depression may alter one's capacity to make treatment decisions, it does not preclude the ability to make some decisions. She expresses a concern that clinicians are often reluctant to respect requests to limit treatment from depressed individuals because the physician perceives limitation of treatment to be assisting a suicide. People with potential for recovery from a period of significant physical or emotional pain or disability should clearly be given the time and treatment they need to facilitate such a recovery. Many older persons' situations will not improve, however, and as Lee states, "When suffering is unlikely to abate, a decision that death is preferable to life may not necessarily be unreasonable" (8). This is clearly a topic that warrants more discussion and research. However, no one has reflected more on a person's life than the person who has lived it, and others must not be too quick to take away the ability to control that life for dubious reasons.

The Role of Advance Directives

Once the medical evaluation is complete and the decision-making capabilities are determined, the next goal is to ascertain the wishes of the patient. This is relatively straightforward for a person with capacity; however, approximately 50% of nursing home residents have some form of mental impairment that may preclude the ability to provide this information (9). Here is where advance directives and prior discussions with friends and family become paramount.

The two most commonly recognized forms of advance directives are the living will and the durable power of attorney for health care. The durable power of attorney is equivalent to the proxy designation in New York State. The main problem with advance directives in general is that only a minority of people use them (10). Therefore, most requests by family members to withhold or withdraw treatment from nursing home residents are not supported by directives. This necessitates the exploration of other forms of evidence, such as recollections of conversations with the resident when he or she had capacity about end-of-life treatment or recollections of how he or she responded to any similar medical conditions and treatment decisions of friends or relatives.

Problems with Living Wills. Even when living wills exist, many of them—especially older documents—tend to be vague and generally do not satisfy the standard of "clear and convincing" evidence. Documents several years old often raise concerns about whether the person may have changed his or her mind about refusing treatment, especially when the treatments seem relatively commonplace, such as antibiotics.

In a recent *Hastings Center Report,* John Robertson expressed his belief that many physicians are justified in not taking living wills seriously. When we become incompetent, we really become different people, with different needs and interests that we really cannot appreciate ahead of time. Accordingly, directives written by competent persons for periods of incompetence should be suspect. Robertson suggests that only family members and physicians can assess what our needs and interests are as they observe us in our incapacity (11).

However, this is not the generally accepted view. Although it is recommended that living wills be reviewed periodically and that review be somehow documented, many people spend years in a state of incapacity and can no longer exercise this safeguard. The fact remains that for those who have one, the living will is the best evidence we have of their wishes. We should not presume that someone may have changed his or her mind about care, absent any evidence to that fact.

Advantages of Proxy Appointments. The limitations of living wills—the applicability of patient preferences to current situations, vague wording, and so on—have led many people to believe that, when filling out an advance directive, a proxy designation is preferable, for it is more flexible, empowering someone to address the vagaries inherent in living wills. Although it is anticipated that more and more people will utilize these directives, the evidence is ample that the current generation of elderly persons will continue to rely on family for decision-making, without understanding that their families are not necessarily empowered to speak for them when they can no longer speak for themselves (12). Even when proxy documents are in place, many studies have challenged whether surrogate decision-making can ever achieve the goal of substituted judgment, absent the coexistence of more detailed documentation of wishes (13, 14). Nevertheless, trying to ascertain the wishes for treatment of a nursing home resident remains the ideal.

Artificial Nutrition And Hydration

Clearly, the request in the nursing home that invokes the most debate and turmoil among staff is to withhold or withdraw nutrition and hydration administered via a nasogastric or other type of feeding tube. Some of the debate hinges on legal requirements that nursing homes provide adequate nutrition and hydration to all nursing home residents. In New York State, for example, failure to do so, except under carefully detailed circumstances, is regarded as resident abuse. Beyond that is the feeling of many health care providers that in almost all circumstances, being fed is routine care that should never be refused or denied. In spite of court decisions, including the Cruzan decision, which characterized tube feedings as "treatments" that could be refused like any other treatment, tube feedings are often not seen as such (1).

In addition to presenting a moral dilemma, consideration of tube feedings again has to involve a rigorous medical evaluation. In an elderly person, loss of appetite is one of the most common symptoms of a myriad of disorders, ranging from fecal impaction and urinary tract infection to drug reactions. Again, staff members sometimes too easily feel there are no alternatives to tube feeding, and families sometimes too easily feel that the resident warrants no further treatments, even when the cure may be relatively simple, and adequate evaluation and treatment will restore the resident to begin eating on his or her own again. A prompt and thorough medical evaluation is necessary in the first case before tube feedings are instituted, whereas in the second situation a time-limited trial can often be helpful.

In situations where the "clear and convincing" standard is met and tube feedings may legitimately be refused, uncertainty may remain about the resident's status and the family or the agent's level of comfort with the request to withhold tube feedings. The ethically acceptable approach is to try treatments that may prove beneficial and withdraw them if they fail to achieve their goals. There is no ethical or moral distinction between withholding and withdrawing a treatment, nor is there a legal distinction. Ethicists feel the general rule is, When in doubt, treat, then deliberate and withdraw the treatment if it is deemed either ineffective or inappropriate. In most cases, the psychological burden this places on staff and family can sometimes be outweighed by the knowledge that the treatment was tried and did not achieve its goal.

Conclusion

Even when a nursing home resident's wishes are clear and a medical evaluation reveals the resident to be in a condition in which wishes to forgo treatment should be respected, several other issues must be addressed. Caregivers, in particular physicians and nursing staff, may have personal disagreements with the choices made by the resident. It is imperative that all staff who will be involved in the implementation of a decision to withhold or withdraw treatment from a nursing home resident, or from any patient, are included in the decision-making process. Even if they disagree with the final outcome, knowing how a decision was reached and knowing that it truly reflects the wishes of the resident can only make providing the comfort-care needed easier.

More important, whenever possible, staff who will be faced with difficult decisions about patients at the end of life should be educated about ethical issues and involved in the development of institutional policies that guide decisions to withhold or withdraw treatments.

Finally, staff also need to be educated in comfort-care issues and also need emotional support to assist them as they care for residents for whom treatments are being withheld. Most nursing home staff develop close relationships with the residents for whom they care, and this, coupled with perceived professional obligations to always support life and with conflicts with decisions made by others to forgo treatments, can make caring for these residents very difficult. Emphasizing that respect for resident autonomy is one of the greatest gifts staff can give to those for whom they care may ease their concerns.

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Nursing Staff Attitudes on the Use of Physical Restraints in a Teaching Nursing Home

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Staff in hospitals and nursing homes in the United States, unlike staff in European facilities, routinely use physical restraints on patients (1). Before the Omnibus Budget Reconciliation Act (OBRA) became effective in October 1990, throughout the United States 500,000 older Americans were tied to their hospital or nursing home beds and chairs (2). About half of all New York State nursing home residents were physically restrained at least part of each day (1). The OBRA-defined federal regulations on nursing homes on the use of restraints in health-care facilities specified the rights of each resident to be free from physical or chemical restraints imposed for purposes of convenience and not required for treating a resident's symptoms (3).

Prolonged immobilization of the elderly contributes to such physical disabilities as disordered motor function, contractures of joints, edema, decubitus ulcers, and incontinence; it also contributes to many behavioral outcomes, such as depression, social withdrawal, apathy, and anxiety (4). Strumpf and Evans interviewed 20 restrained hospitalized elderly patients and found their responses to be primarily fear, demoralization, discomfort, anger, humiliation, and denial (5). McHutchion and Morse note that initially restrained patients are angry and sometimes hostile and eventually develop progressive physical and emotional deterioration (6).

Despite awareness of the negative outcomes of physical restraints, they continue to be used in the United States. Some investigators have suggested that few alternatives exist (5) and that restraints are most commonly used to protect patients (2). Others have classified the reasons for restraining the elderly as "external" and "internal." According to McHutchion and Morse, external situations include those in which staff feel they have little control, experience pressure from families, and fear being liable should a fall occur; staff's internal or intrinsic reasons for using restraints include beliefs about lack of alternatives and safety issues and perceptions that using restraints saves time (6). Similarly, Williams considers such factors as staff attitudes, staffing ratios, and ideas about risk being correlated with restraint use (1).

This study assesses the attitudes of a large population of nursing assistants and licensed nursing staff toward using physical restraints in a long-term-care facility and explores staff perceptions of the effects of restraints. The study hypothesizes that intrinsic and extrinsic factors are associated with recommendations to apply physical restraints in various clinical situations. In addition, the potential effect of formal nursing education is explored.

Setting, Study Subjects, And Methods

Setting. The Jewish Home and Hospital for Aged (JHHA) is the teaching nursing home affiliated with The Mount Sinai Medical Center in New York City. There are two campuses: a Manhattan division consisting of 514 beds, and a Bronx division of 816 beds. The academic faculty

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at the JHHA hold academic appointments in the Department of Geriatrics and Adult Development at Mount Sinai Medical School. Geriatrics fellows and fourth-year medical students do clinical rotations at JHHA.

As of May 1990 the nursing home residents had an average age of 83 years (**Table 1**); about one-third were physically restrained.

Methods. In this study, physical restraints are defined as any device that binds or surrounds the resident and is used to restrict movement. Examples include mittens, waist restraints, criss-cross belts and straps to tie down hands, and chairs that prevent rising. For this study, bed rails were considered possible accident hazards but not physical restraints.

Nursing staff include all personnel involved in the direct care of the nursing home residents: licensed staff and nursing assistants (aides and orderlies).

A questionnaire was developed consisting of 40 items on extrinsic and intrinsic factors that potentially contribute to restraint use; the perceived effects of restraint use; and situations in which physical restraint use might be recommended. Nursing staff were asked to circle the appropriate number on a 5-point Likert scale (1, strongly agree; 2, agree; 3, uncertain; 4, disagree; 5, strongly disagree).

A pilot study was conducted on two units that had minimized restraint use within the year prior to the study and on two units that were in the process of minimizing restraint use. The questionnaire was pretested in the pilot study and refined as a result.

Extrinsic factors that potentially contribute to restraint use were operationalized as concerns about the job, the environment, and safety. Intrinsic factors that potentially contribute to restraint use were operationalized as attitude toward restraint use and toward residents. The perceived effects of restraint use were operationalized as physical, emotional, and behavioral effects and relationship to use of psychotropic medications.

In addition, a series of seven clinical situations was presented; respondents were asked to indicate, on a 5-point Likert scale, the likelihood that they would recommend the use of physical restraints under various conditions (for example: "I would recommend the use of physical restraints for the following: a resident who is confused; a resident who physically hurts himself or others; a resident who pulls out an intravenous or nasogastric tube . . ."). Each item was examined separately in comparing attitudes of licensed nurses to those of nursing assistants. To obtain a global view of the tendency to use restraints, responses to the seven situations were added together. By using multiple regression, this index of overall tendency, which took on values ranging from 7 to 35, served as the dependent variable for examining which characteristics and attitudes were most strongly related to the tendency to use restraints.

The 40-item questionnaire was distributed at various staff meetings to all nursing personnel on all three shifts (day, evening, and night) at both the Manhattan and Bronx facilities. One investi-

TABLE 1

Characteristics of Residents of The Jewish Home and Hospital for Aged, May 1990

Characteristic	Manhattan campus	Bronx campus
Total no.	514	816
No. of SNF	476	646
Average age	83 years	83 years
Average length of stay	2.3 years	2.9 years
% male	20%	18%
% female	80%	82%
% physically restrained	32%	35%
% taking psychotropic medication	40%	47%
Most common diagnoses on admission	OMS/dementia Post-status stroke	OMS/dementia Coronary artery disease

TABLE 2

Characteristics of Nursing Staff of The Jewish Home and Hospital for Aged

Characteristic	N	Percentage
Job Title		
Licensed staff	82	31%
Nursing assistants	186	69%
Shift		
Day	142	52%
Evening	79	29%
Night	52	19%
Education		
Some high school	22	10%
High school grad	84	37%
Some college	44	20%
2-year college degree	33	15%
4-year college degree	19	8%
Graduate degree	22	10%
Years employed at facility		
<2 years	40	16%
2–4 years	36	15%
≥5 years	167	69%
Place of birth		
United States	53	31%
Outside U.S.	117	69%

TABLE 3

Likert Scores‡ of Nursing Home Staff by Job Title on Factors Contributing to Attitudes on Restraint Use (Mean ± SD)

Contributing factors	Licensed (N = 82)	Assistant (N = 186)	All staff (N = 268)
Extrinsic			
Job concerns			
Increased work load	2.3 ± 1.1	2.5 ± 1.3	2.4 ± 1.2
Risk of liability	2.6 ± 1.3	2.3 ± 1.4	2.4 ± 1.4
More staff	1.7 ± .89	1.9 ± 1.1	1.8 ± 1.0
Closer supervision	1.3 ± .48	1.5 ± .67*	1.5 ± .65
Feel better about job	3.1 ± .95	3.2 ± 1.0	3.2 ± .97
Environment			
Layout of unit suitable	3.0 ± 1.2	2.8 ± 1.3	2.9 ± 1.2
More alarm/adaptive devices	1.6 ± 6.1	2.0 ± 1.0†	1.9 ± .92
More activities	1.9 ± .83	2.0 ± .91	2.0 ± .87
Safety concerns			
Safety of residents jeopardized	2.3 ± 1.1	2.2 ± 1.1	2.2 ± 1.0
More falls of residents	2.2 ± .98	1.1 ± 1.1	2.1 ± 1.1
Staff harmed	3.6 ± .99	3.4 ± 1.1	3.5 ± 1.0
Residents would wander	2.7 ± 1.1	2.5 ± 1.1	2.6 ± 1.1
Residents feel safer restrained	3.5 ± .89	3.3 ± 1.1	3.3 ± 1.1
Intrinsic			
Attitude to restraint use			
Invasion of basic right	2.9 ± 1.1	2.7 ± 1.3	2.8 ± 1.2
Even if risky, worth a try	2.1 ± .67	2.3 ± 1.3*	2.3 ± .90
Restraints in use necessary	2.5 ± 1.0	2.5 ± 1.2	2.4 ± 1.1
Residents never restrained	3.9 ± 1.0	3.8 ± .94	3.9 ± .92
Attitude to residents			
Aware of residents' needs	1.6 ± .64	1.8 ± .83	1.7 ± .75
View job as caring/helping	1.6 ± .74	1.6 ± .75	1.6 ± .71
Encourage resident self-help	1.7 ± .81	1.6 ± .70	1.6 ± .72
Perceived effects of restraint use			
Physical			
Interfere with medical treatment	3.8 ± .85	3.7 ± 1.0	3.7 ± .94
Debilitating conditions	2.6 ± 1.1	2.8 ± 1.1	2.8 ± 1.1
Emotions of residents			
Angry	2.3 ± .91	2.2 ± 1.1	2.2 ± 1.0
Fearful	2.6 ± 1.0	2.6 ± 1.1	2.6 ± 1.1
Humiliated	2.5 ± .87	2.4 ± 1.1	2.4 ± .97
Discomfort	2.3 ± .91	2.1 ± 1.0	2.2 ± .98
Helpless	2.3 ± .87	2.2 ± .94	2.3 ± .94
Less calm	—	—	2.6 ± 1.0
Trapped	2.2 ± .79	2.5 ± .95*	2.2 ± .90
Behavior of residents			
Less agitated	3.4 ± .87	3.5 ± 1.1	3.7 ± 1.0
More dependent	2.4 ± 1.1	2.8 ± 1.2†	2.7 ± 1.2
Calm	2.6 ± 1.0	2.5 ± 1.1	—
Use of psychotropic medications			
If taking, likely to be restrained	3.4 ± 1.0	2.5 ± 1.1†	2.8 ± 1.1
Given less if restrained	3.6 ± .94	3.3 ± 1.1	3.4 ± 1.1

* <.05; † <.001.

‡ 1, Strongly agree; 5, strongly disagree.

gator attended various shift meetings to explain and distribute questionnaires. All nursing personnel working at that time were included in the study if they worked on the units where efforts to minimalize restraints had not yet occurred. Surveys were also distributed at in-service education meetings. Per diem staff, "floating" staff, and nursing personnel on vacation at the time of the survey distribution were not included. Since English is a second language for many respondents, the questionnaire items were read to a considerable number of them.

The data for this study come from the responses of 268 nursing personnel (**Table 2**), 69% nursing assistants and 31% licensed staff, all working on units where physical restraints are used; none had been exposed to restraint-free efforts. All shifts are appropriately represented. About 90% were at least high school graduates, and one-third had at least a two-year college degree. Not all staff completed the questions on education level and place of birth. The majority of staff (69%) had been employed at the JHHA five years or more. Most were born outside the United States, the greatest percentage originating in the West Indies.

Results

Attitudes. Most nursing staff believe that if the use of physical restraints were reduced, their work load would increase, they would be at greater risk of liability, units would require more staff, and residents would require closer supervision (Table 3). They are uncertain about whether they would feel better about their jobs.

Most agree that more alarm devices and activities would be needed if use of physical restraints were reduced. Staff are uncertain if the layout of the units where they work is suitable for restraint-free residents to move around in. Most also agree that resident safety would be jeopardized if restraint use were reduced, because residents would fall more frequently, but staff are uncertain if residents would be more likely to wander. They are also uncertain about whether residents feel safer when restrained. They do not believe that residents would more easily harm staff if restraint use were reduced.

Most agree that reducing restraint use is worth a try, even if these efforts may be risky; however, they view the majority of restraints currently in use as necessary, because there are circumstances in which residents may require physical restraints. The majority of staff consider themselves aware of residents' needs and view caring for and helping residents and encouraging them to help themselves as the job of nursing staff.

On the perceived effects of restraint use, most staff feel that restraints can be reduced without interfering with medical treatment, but they are uncertain whether residents develop more debilitating conditions when physically restrained.

Most agree that residents become angry and feel humiliated, uncomfortable, helpless, and trapped when restrained, but are unsure if residents become fearful. Most believe that residents would be less agitated if restraints were reduced but are uncertain whether residents are more dependent when physically restrained or calmer when restraint-free.

Survey responses indicate that staff are uncertain about whether residents taking psychotropic medications would be more likely to be restrained. They are also uncertain if residents would be given more psychotropic medications should restraint use be reduced.

Overall, the attitudes and perceptions of licensed staff are quite similar to those of nursing assistants (Table 3). However, licensed staff tend to have fewer concerns about resident safety and are also less likely to view a reduction in restraint use as interference with the medical treatment of residents.

Although the attitudes and perceptions of nursing assistants are similar to the views of the licensed staff whatever the situation or status of a particular resident (Table 4), questionnaire responses indicate that, given the opportunity, nursing aides are more inclined to use restraints in all situations.

Multiple regression analyses identified nursing assistant status as more strongly associated with a tendency to recommend restraint use than licensed status; this status was the factor most predictive of a tendency to use restraints. Other such predictors were working the night shift; fearing being more easily harmed; viewing the job role as primarily taking care of and helping residents; believing residents' safety would be jeopardized by reduction in restraints; and being more apt to restrain residents taking psychotropic medications.

Discussion

This study supports the hypothesis that intrinsic (attitudes toward restraint use) and extrinsic (safety, environmental, and job concerns) factors contribute to the nursing staff's desire to use physical restraints. In addition, the staff believe that restraints contribute to negative physical, behavioral, and emotional changes in residents.

TABLE 4

Likert Scores§ of Nursing Staff by Job Title on Recommendations for Restraint Use (Mean ± SD)

Resident's status	Licensed (N = 82)	Assistant (N = 186)
Confused	3.3 ± 1.0	2.6 ± 1.2‡
Physically harms self/others	2.1 ± .87	1.9 ± .86
Pulls out IV/NG tube	2.0 ± .68	1.9 ± .86
Left unattended in toilet	3.4 ± 1.2	2.9 ± 1.2†
Gets out of bed by self	3.5 ± 1.0	3.0 ± 1.2†
Slides out of chair	2.4 ± 1.1	2.1 ± .92*
Falls frequently	2.2 ± 1.0	2.0 ± .96*

* <.05.

† <.01.

‡ <.001.

§ Lower scores indicate greater likelihood of recommending restraint use.

A major finding of the study is the identification of factors that contribute to recommendations of restraint use. The most significant factor appears to be the perception that the staff would be harmed and the safety of residents would be jeopardized if restraints were reduced; also significant is that staff working the day shift are less likely to recommend physical restraints than are those working the evening and night shifts.

These findings are consistent with the literature, including the finding that agitated patients are frequently medicated and physically restrained. Evans and Strumpf report that prevention of injury to self or others is the most frequently cited rationale for the use of physical restraints (7). Agitated patients can be abusive to themselves as well as to others. Investigators such as Catchen (8) report that most accidents involve wheelchairs and occur during the day, whereas the most serious falls occur out of bed at night. Therefore, it is understandable why the JHHA staff who work the day shift—when more staff members are present—would be less likely to recommend restraints; serious falls are less likely to occur on their shift.

The finding that licensed staff are less likely to recommend restraints suggests that nursing education might usefully develop different programs that address the specific needs of both the licensed staff and nursing assistants. Another consideration is that nursing assistants have direct contact with patients and may feel more responsible if an injury occurs once restraints are removed. They also have lower status than licensed staff and may be inhibited or uncomfortable about initiating such a change as removing a restraint. The fact that many were unwilling to divulge personal information suggests fear of reprisal or lack of confidence.

Summary and Conclusions

This study supports the importance of assessing the intrinsic and extrinsic attitudes and perceptions of staff on physical restraints. Any program developed to remove physical restraints in nursing homes should focus on safety issues and behavioral interventions that prevent injury to staff and resident. Environmental adaptations that would enhance residents' safety, such as alarms and wedge cushions, would be useful in a restraint reduction program. Educating staff about the risks of physical restraints and about safe alternative interventions might change their attitudes. By developing an educational program that focuses on a few residents at a time and by involving a multidisciplinary team, a truly individualized approach to restraint-free care for residents might be developed.

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Research Activities in the Department of Geriatrics and Adult Development

JOHN H. MORRISON, PH.D., JON GORDON, M.D., PH.D., MYRON MILLER, M.D., HOWARD FILLIT, M.D., AND DIANE E. MEIER, M.D.

SINCE ITS ESTABLISHMENT ten years ago, the Department of Geriatrics and Adult Development at Mount Sinai Medical Center has always had a major commitment to its research programs. These programs cover a wide spectrum, from the molecular biology and neurobiology of aging to age-related changes in bone homeostasis in humans. The research activities of the department include laboratories housed entirely within the department and laboratories established through liaisons with other departments at Mount Sinai Medical School interested in the biology of aging. The activities and interests of the five major research programs within the department are summarized below.

Molecular Genetics of Neurodegeneration: Transgenic Studies of Superoxide Dismutase

Jon Gordon, M.D., Ph.D.

One of the few surviving theories of aging is the oxygen-free-radical theory, which postulates that aging is a manifestation of cumulative oxygen-free-radical damage to macromolecules. Examples of such damage include lipid peroxidation and mutations of DNA. Although it is unlikely that this or any other single hypothesis will explain all aspects of aging, evidence is accumulating that oxygen-free radicals may play an important role in the decline of function in the central nervous system (CNS): Humans or experimental animals with altered expression of Cu/Zn superoxide dismutase (SOD-1), a key enzyme in the oxygen-free radical scavenging system, exhibit either accelerated or delayed degenerative changes in the CNS. For example, transgenic mice with increased expression of SOD-1 are resistant to drug-induced neurodegeneration, and humans carrying a variety of point mutations in the SOD-1 gene are subject to familial, autosomal dominant amyotrophic lateral sclerosis (FALS), an age-related degenerative disease that mainly involves motor neurons.

One of my major research objectives is to clarify the relationship between oxygen-free radicals and aging in the CNS. My laboratory has cloned the mouse genomic sequence encoding SOD-1 (1), and was also the first laboratory to produce a transgenic mouse (2). I and my colleagues have now produced transgenic mice carrying additional copies of the mouse SOD-1 gene. These animals are currently being studied for expression of the foreign gene, and will ultimately be examined for lifespan and resistance to damaging effects of oxygen-free radicals.

In addition, my group has created mutant SOD-1 genes that correspond to the mutant genes found in humans with FALS. These modified genes will be microinjected into pronuclear stage embryos (2), and resultant transgenic mice will be studied for neurodegenerative disorders.

Finally, I am employing targeted mutagenesis in embryonic stem (ES) cells to destroy the SOD locus. With the ES cell system, it is possible to substitute mutated, inactive genes for endogenous mouse loci by homologous recombination.

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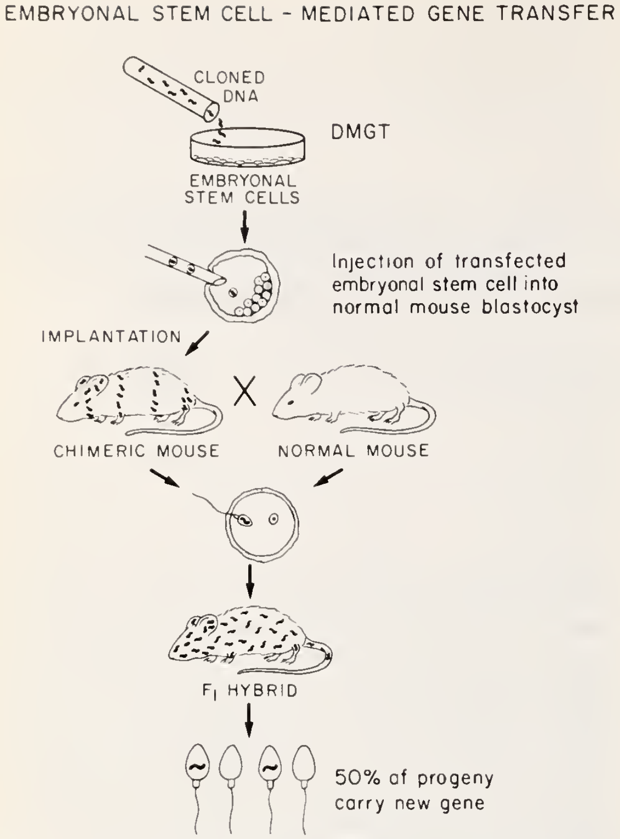
EMBRYONAL STEM CELL - MEDIATED GENE TRANSFER
CLONED DNA
DMGT
EMBRYONAL STEM CELLS
Injection of transfected embryonal stem cell into normal mouse blastocyst
IMPLANTATION
X
CHIMERIC MOUSE
NORMAL MOUSE
F₁ HYBRID
50% of progeny carry new gene

Fig. 1. Production of transgenic mice by use of embryonic (embryonal) stem (ES) cells. ES cells are maintained in culture and subjected to DNA-mediated gene transfer (DMGT, top), for insertion of genes or gene substitution by homologous recombination. Transformed cells are then injected into the cavity of a normal mouse blastocyst and implanted. The resulting mouse is a genetic chimera that often has a striped coat (center). If these chimeras, usually males, produce sperm derived from the ES cells, an F_1 hybrid mouse carrying the genetic modification in all cells can be produced (bottom). This animal can then be bred to establish a new transgenic strain.

The ES cells with such genetic modifications can then be inserted into the cavity of a normal mouse blastocyst, whereupon they can be induced to resume normal development and give rise to normal tissues of adult, genetically mosaic mice. If ES cell derivatives colonize the germ cell population of a chimera, the genetically engineered mutation can be transmitted to progeny to establish mutant strains of animals. The scheme for construction of transgenic mice by the ES cell approach is outlined in **Fig. 1**.

Animals carrying mutated, functionally inactive SOD-1 genes should provide important new insights into the role of oxygen free radicals in aging. Further experiments include use of microinjection and homologous recombination to replace the normal murine SOD-1 locus with SOD-1 genes that have been modified in vitro to carry mutations specific for FALS in humans. Studies of transgenic mice constructed carrying the altered genes should help clarify the relationship between altered SOD-1 activity and neurodegenerative disorders such as ALS.

My laboratory is also using transgenic technology to determine whether modifications of SOD-1 expression actually affect the mutation rate in vivo. For these experiments, my laboratory colleagues are inserting genes that can be recovered from the animals by molecular cloning and conveniently screened for the presence of mutations. These "mutation monitor genes" will be inserted into the strains with modified SOD-1 genes by breeding, and then animals with both genes will be studies for mutations accumulation.

Age-Related Changes in Neuroendocrine Function

Myron Miller, M.D.

Overproduction of the posterior pituitary hormone vasopressin occurs during aging in humans and in animals as part of the normal aging process and as a result of a number of diseases (3, 4). Thus, the development of animal models of increased vasopressin production can allow studies to be carried out which will help clarify the impact of increased hormone secretion on a variety of systems during the course of aging. One focus of research has been studies of the physiology and pathophysiology of fluid and electrolyte disturbances, which are common in the aged and may have significant clinical consequences, including alterations in central nervous system function.

Through application of transgenic technology, we in my laboratory have created a transgenic mouse model of chronic vasopressin hypersecretion (5–7). In this animal, the rat gene for vasopressin has been incorporated into the mouse genome. Data obtained clearly demonstrate that the transgenic rat gene functions in the mouse and that the transgene is capable of producing vasopressin in tissue sites where the hormone is normally expressed (5, 6). Thus, it has been demonstrated that increased vasopressin synthesis takes place in the hypothalamus of the mouse as well as in the cerebral cortex (Fig. 2). As a consequence of transgene function, increased amounts of vasopressin are secreted into the peripheral circulation and are excreted into the urine. Data demonstrate that the level of overproduction of the hormone is approximately three to five times that which would occur in a normal mouse (Fig. 3).

Physiological studies in the transgenic animals have demonstrated that the incorporated transgene responds in a normal fashion to challenges which lead either to stimulation or suppression of hormone production. There is some evidence that chronic exposure to increased amounts of vasopressin results in activation of compensatory systems for body water regulation so that chronic hormone overproduction does not lead to fluid overload. In addition, there is evidence suggesting that chronic exposure of the blood vessels to vasopressin leads to a reduction in blood pressure, again suggesting that compensatory mechanisms may develop to offset the acute effects of the hormone (7).

Previous work from this laboratory has established that vasopressin is capable of affecting central nervous system activity by modifying brain functions involved in expression of learning and memory ability (8). We have now conducted studies in the transgenic mice which demonstrate that these animals with chronically increased hormone secretion alter their behavior in the direction of increased arousal and increased ease of adaptation to new environments (9). These observations raise the possibility that vasopressin or its analogs may have therapeutic benefits in treatment of cognitive disorders.

In addition to the animal studies, clinical research has been conducted on the influence of aging on hormonal systems involved in water regulation. We have demonstrated that the production of atrial natriuretic hormone, a substance involved in sodium regulation in the body, is increased during normal aging and that secretion of this hormone is markedly increased following exercise. These observations have been utilized in studies evaluating hormonal function during congestive heart failure to examine the role of altered hormone secretion in the fluid disturbances which are so prevalent in this disorder.

Other clinical investigations have focused on the regulation of vasopressin release in individuals with various types of dementia. Since cholinergic deficits are characteristic of patients with Alzheimer's disease and since cholinergic mechanisms are involved in the regulation of vasopressin synthesis and release, there is reason to suspect that patients with Alzheimer's disease may have alterations in their ability to regulate vasopressin. Studies are currently under way to determine if hormonal responses to cholinergic-mediated stimuli will be helpful in differentiating patients with Alzheimer's dementia from those with dementia of other cause.

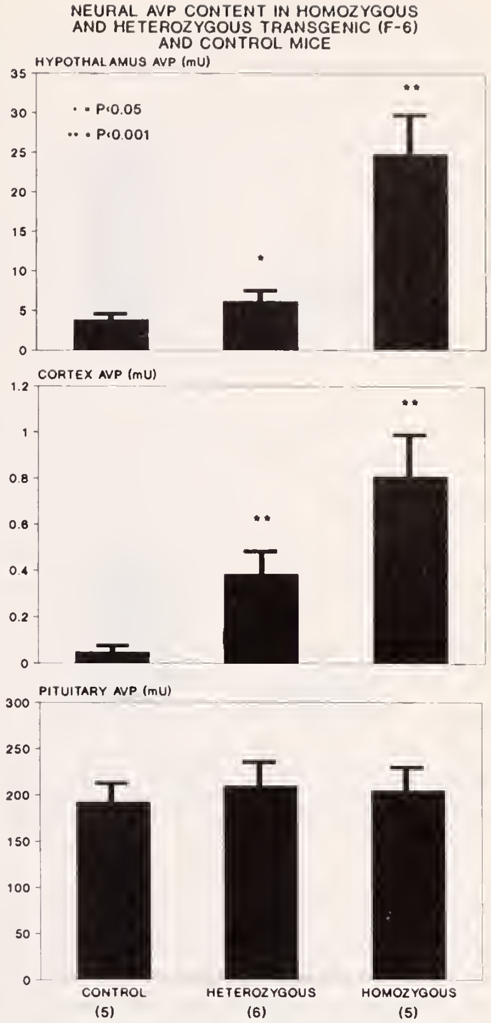

Fig. 2. Arginine vasopressin (AVP) content in the hypothalamus and frontal-temporal cortex is significantly increased in both heterozygous and homozygous transgenic mice, being greater in homozygous than in heterozygous tissues. There were no differences in pituitary AVP content.

Neuroanatomic and Molecular Determinants Of Vulnerability in Alzheimer's Disease

John H. Morrison, Ph.D.

Much of the research in my laboratory involves trying to link molecules that have been implicated in neuronal degeneration to the cells and circuits that are at risk in Alzheimer's disease (AD). For example, a wide range of both qualitative and quantitative studies on the distribution of neuritic plaques (NP), neurofibrillary tangles (NFT), neuron loss, and synapse loss suggest that there are two classes of cortical circuits particularly devastated in AD: (a) the corticocortical projections within neocortex that link the association areas of prefrontal, temporal, parietal, and limbic cortices; and (b) the parahippo-

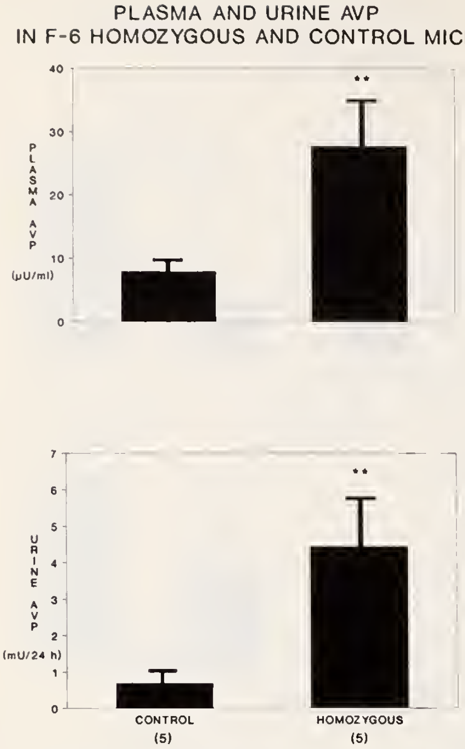

Fig. 3. Both plasma arginine vasopressin (AVP) concentration and urinary AVP excretion are significantly increased in transgenic mice homozygous for the rat AVP gene.

campal and hippocampal circuits that project from the entorhinal cortex to the hippocampus, as well as those that provide the primary outflow from the hippocampus to related cortical areas (10). Although it is clear that the pyramidal cells furnishing such projections suffer a devastating loss in AD, the cellular and molecular basis of such differential vulnerability in AD or any other neurodegenerative disease is less clear. I and my colleagues have hypothesized that neuron classes and circuits that possess heightened vulnerability to the neurodegenerative process underlying AD are likely to possess a unique neurochemical profile that is both essential to their particular role in cortical function, and causally linked to their vulnerability in AD and other neurodegenerative disorders (11). More specifically, the neurochemical and cellular attributes of pyramidal cells in neocortex that furnish long corticocortical connections and are presumably crucial for that particular highly developed, specialized role in neocortex might also be linked to their vulnerability. Many of this laboratory's current efforts are directed at developing quantitative neuropathologic and experimental data that test this hypothesis and reveal the critical cellular and molecular links to both normal function and vulnerability in both neocortex and hippocampus.

Recent studies have demonstrated striking correlations between the presence of certain proteins, such as neurofilament protein (NFP), and vulnerability in AD, whereas other proteins, for instance calcium-binding proteins (CABP), have been associated with resistance to degeneration. In the case of NFP, several factors link the presence of this class of cellular proteins to vulnerability in AD:

First, pyramidal cells that contain particularly high levels of the NFP triplet are highly prone to degeneration or NFT formation in the neocortex of AD patients (12–14).

Second, the neurons that appear to exhibit the highest level of vulnerability in AD, the layer II neurons of the entorhinal cortex, contain particularly high levels of the NFP triplet, and NFPs are present in the transitional forms of the NFT that can develop in these neurons during normal aging (14).

Third, transgenic animals that contain the human gene for the middle molecular weight neurofilament subunit, NF-M, display several reflections of pathology associated with human neurodegenerative disorders, one of which is very similar to the NFT seen during normal aging and AD (15).

In addition, NFP are selectively present in certain subgroups of neurons that furnish corticocortical projections across association areas in monkeys which are also likely to correspond to the subgroup of projection neurons that are particularly vulnerable in AD (16) (for example, temporal to prefrontal projection neurons). The CABPs parvalbumin, calbindin, and calretinin may play an important role in conferring resistance to degeneration on a particular subset of neurons. The interneurons containing any one of these three proteins have been shown to be resistant to degeneration in both AD and ischemia (see ref. 10 for review), and these proteins may buffer intracellular calcium, thereby protecting a neuron from calcium-mediated excitotoxicity.

Recently, laboratory staff members turned their attention to the glutamate receptors (GluRs), both for intrinsic interest in respect to excitatory circuits in cerebral cortex, and as a third group of proteins that might be a critical element in a neurochemical profile of vulnerability for AD as well as other neurodegenerative disorders, such as ALS or ischemia. Recent developments in glutamate receptor neurobiology suggest that while excitatory circuits and glutamate receptors might be ubiquitous in the cerebral cortex, clearly the molecular diversity exists to allow for extraordinary specificity in the postsynaptic profile of a given excitatory circuit.

Thus, a more specific version of the hypothesis stated above could be developed in that particular GluR subunit combinations and GluR family interactions might subserve a subset of excitatory circuits in the cerebral cortex, and both the presence of and putative age-related shifts in such profiles might be linked to differential vulnerability of certain circuits in disease states such as Alzheimer's disease. Glutamate-receptor-mediated excitotoxicity has not only been linked to neurodegenerative disorders as a powerful mechanism for neuron death, but, more specifically, has been linked to alterations of the cytoskeletal proteins that are implicated in NFT formation. With the use of riboprobes and subunit specific antibodies, it is now feasible to characterize in detail the GluR specificity linked to identified excitatory cortical circuits, and develop detailed subunit- and family-specific GluR profiles of both vulnerable and resistant neurons that will reveal the degree to which certain GluR subunits exhibit circuit-linked specificity and might be implicated in the differential vulnerability apparent in neurodegenerative disorders. Thomas Moran of the Hybridoma Core Facility at Mount Sinai and I have in collaboration generated several monoclonal antibodies to various glutamate receptor subunit proteins. Double labeling studies have shown that the neurofilament-containing neurons that are vulnerable to degeneration in AD also contain the subunits that form kainate and AMPA receptors (17). The studies with the antibody to kainate subunits demonstrated marked variability in density and distribution of kainate receptor immunoreactivity across layers and areas of monkey neocortex.

These results indicate that GluR5/6/7 subunit immunoreactivity appears to be more dense in higher-order association areas of the frontal and parietal lobes than in the primary sensory areas SI and V1 (18). These qualitative observations were confirmed quantitatively by comparing the densities of stained somata in areas 9, V1 and V2. These data raise the possibility that the functions of higher-order association areas may be particularly vulnerable to kainate receptor-mediated toxicity. Similar analyses are now under way for AMPA and NMDA receptor subunit distribution in neocortex and hippocampus.

Proteoglycans in Vascular and Other Diseases

Howard Fillit, M.D.

Role in Vascular Disease. Vascular heparan sulfate proteoglycans (vHSPG) play an important role in the structure and function of the vasculature, including endothelial cell adhesion and basement membrane structure, vascular permeability barrier integrity, normal hemostasis, lipolysis, and vascular repair (19). Vascular heparan sulfate (HS), a glycosaminoglycan, plays a major role in the capillary permeability barrier (20). HS also plays an important role in the delicate balance of coagulation through a variety of mechanisms which ultimately, at least in part, inhibit thrombin activity. Endothelial vHSPG binds antithrombin III (21) and enhances the inhibition of thrombin more than a thousandfold through the formation of a ternary complex. Thus, heparan sulfate is the native molecule on the endothelial cell surface that provides the anticoagulant functions associated with heparin.

Numerous studies have demonstrated that glycosaminoglycans (GAGs) such as hyaluronate, chondroitin sulfate, heparin, and heparan sulfate are both immunogenic and immunospecifically antigenic. Recently, monoclonal antibodies specific for heparan sulfate (16, 22–24) and heparin (25), a GAG related to heparan sulfate, have been reported. Fillit and others have described autoantibodies to GAGs which are reactive with specific antigenic determinants of HS and heparin (16, 22–27).

Studies of autoimmunity to HS, including both active (28) and passive transfer (29) immunization models, the presence of the pertinent antibody at the site of injury in animals and humans with the disease (30, 31), and a correlation of the antibody with clinical disease activity (31, 32) essentially fulfill the criteria necessary to demonstrate that autoantibodies to HS GAG are pathogenic (33). Of interest, heparin treatment of animals with vascular autoimmunity neutralizes autoantibodies thought to be responsible for vascular injury (34). Monoclonal antibodies to HS created in my laboratory from autoimmune mice inhibited heparan sulfate accelerated formation of thrombin-antithrombin III complex (23), and thus may promote a procoagulant state and thrombosis, suggesting a noninflammatory immune-mediated mechanism of vascular injury induced by autoimmunity to HS. Finally, in addition to autoimmunity to HS immunodeterminants, antibodies to HSPG protein core immunodeterminants cause vascular injury in animal models (35, 36).

Initial studies have focused on vascular autoimmunity in systemic lupus erythematosus (SLE), an intensively investigated autoimmune disease. These studies have demonstrated autoantibodies to intact vHSPG in patients with systemic lupus erythematosus, including both HS and the protein core components (27, 37, 38). Recent data from this laboratory also indicate the presence of antiheparin antibodies in human vascular disease sera which inhibit formation of TAT complexes (26).

Autoantibodies to vHSPG were also found in aged patients with various forms of vascular disease, including stroke and dementia (38, 39). Walford (40) initially proposed that autoimmunity may play a role in vascular disease during aging. Vascular disease in old age is frequently immunologically mediated (41). In fact, giant cell arteritis, a common immunologic vascular disease of the aged, is associated with degenerative vascular disease (42), and immune mechanisms may cause atherosclerosis (43). Thus, my colleagues and I are continuing to investigate the role of autoimmunity to vHSPG as a cause of vascular disease in the aged.

Role in Amyloidosis and Alzheimer's Disease. Alzheimer's disease (AD) is a neurodegenerative disorder characterized by a loss of large neurons and the extracellular accumulation of amyloid deposits containing a peptide (the A4 peptide) which is derived from a larger amyloid precursor protein (APP). APP probably plays a role in the pathogenesis of AD, either as a primary event or as part of the evolving pathologic process which leads to neuronal loss and dementia (44).

Proteoglycans also play an important role in the brain, including CNS development, neurite outgrowth, and neuronal cell adhesion (45). HSPGs codeposit concurrently with amyloid proteins in senile plaques in AD and other diseases and are thought to play a fundamental role in all forms of amyloidosis (46). Using monoclonal antibodies (mAbs) to vHSPG protein core, the presence of HSPG in senile plaques and in neurons in AD has been demonstrated (47, 48). High affinity binding of different forms of APP to HSPG (49, 50), high affinity binding of both vascular and neuronal HSPG to APP (45, 51), and high affinity binding of HSPG to the A4 peptide actually deposited in senile plaques have all been demonstrated.

Essentially four hypotheses have been put forward as pathological mechanisms in which HSPG may contribute to amyloidosis. These include (a) initiation of fibrillogenesis, (b) enhancement of fibril formation, and (c) decreased amyloid distribution. All of these hypotheses flow from an initial binding interaction between APP/A4 and HSPG. Since APP/A4-HSPG binding appears to be physiologic, abnormalities in APP/A4-HSPG binding may account for the pathological mechanisms cited.

Finally, using monoclonal antibodies to vHSPG as markers of vascular pathology, H. Fillit has investigated the presence of microvascular alterations in Alzheimer's disease. Recent studies have demonstrated statistically significant decreases in microvascular density in regions of the brain affected by AD (52). It is not currently known if these microvascular changes are a primary or a secondary event in the disease process, but in either case could be contributing to neuronal death via the resultant disorder in vascular supply.

Radical Differences in Bone Homeostasis

Diane E. Meier, M.D.

Available data suggest a significantly lower incidence of fracture and higher bone mass in women of African (black) ancestry than in women of European (white) ancestry. Since adult bone loss occurs universally as a function of age, reasons for the racial difference in bone mass and fracture risk are not immediately apparent. Bone mineral content, which correlates with bone strength and fracture risk, is a function of at least two factors: peak bone mass achieved at skeletal maturity and subsequent rates and duration of bone loss. The lower fracture incidence among black women may be due to (a) higher peak bone mass at skeletal maturity, so that despite comparable age-related bone loss, blacks reach the fracture threshold less frequently than whites; (b) age-related bone loss that begins later, is less severe, or occurs in different skeletal sites; or (c) no difference in bone mass and rate of loss in black and white women, but differences in other risk factors, such as frequency of falls.

This study of bone homeostasis in black and white women was initiated with two hypotheses: (a) the racial difference in fracture prevalence is due to detectable racial differences in adult bone homeostasis; and (b) comparison of groups with high and low fracture risk can provide useful insights into the etiology of osteoporosis and provide directions for future research.

Thus, the research was designed to assess the natural history and the determinants of bone loss in a longitudinal study of healthy white and black pre- and post-menopausal women.

Cross-sectional data from this study showed statistically significantly higher radial and vertebral bone mass in healthy black women, both premenopausal and postmenopausal (53). However, there was substantial overlap in bone density between the two races, more than 25% of healthy black women having vertebral bone density below the mean for white women. Furthermore, 5% of the black and 17% of the white women were noted to be below the theoretical fracture threshold, suggesting that there may be a previously unrecognized subgroup of otherwise healthy black women who are at increased risk for osteoporotic fracture. Bone density at both radial and vertebral sites declined significantly as a function of age in both white and black women by cross-sectional analysis.

Recently analyzed longitudinal data from this study reveal statistically significant premenopausal bone loss in both white and black women, a finding which has major implications for the prevention of osteoporosis in an age group previously neglected in epidemiologic prevention studies.

Although both white and black postmenopausal women also demonstrated statistically significant bone loss, among women less than 5 years postmenopausal a significant racial difference in radial (but not spinal) bone loss was observed; radial bone density declined by 1.1% per year in the blacks, versus 2.2% per year in the whites ($p = .05$). This racial differential in early menopausal bone loss is a new observation, and may be of important etiologic significance in the racial disparity in fracture risk.

Several biochemical measures of bone turnover were measured at baseline, including fasting and 24-hour urinary calcium excretion, urinary hydroxyproline, serum alkaline phosphatase, and osteocalcin. Interestingly, in both pre- and postmenopausal women, measures of bone turnover were significantly lower statistically in black than in white women (54). These findings may be reflected in the slower early menopausal bone loss observed in the black subjects of this study.

To evaluate the vitamin D-parathyroid hormone endocrine system and its relationship to racial differences in bone density, serum concentrations of these hormones were measured. Interestingly, and in contrast to previously published results, in these healthy, normal weight, well-nourished middle-class white and black women there were no major differences in 25 hydroxyvitamin D concentration, nor was there any evidence of secondary hyperparathyroidism in the blacks; previous studies have shown low levels of 25 hydroxyvitamin D and associated secondary hyperparathroidism in poor, obese black subjects (55). Overall, these data suggest that the vitamin D-parathyroid hormone endocrine system is not the major etiologic factor contributing to the racial differences in bone density. This finding underscores the importance of conducting racial comparisons in groups which are as comparable as possible for every controllable parameter with the exception of race. In the past, differences which were probably due to socioeconomic status and malnutrition were inappropriately attributed to racial differences.

To assess the impact of exercise on bone density, assessment of habitual physical activity by questionnaire was obtained, revealing a significant correlation between lumbar bone density and average daily weight-bearing activity in both white and black women. However, the racial differences in bone density observed in these subjects could not be statistically accounted for by differences in physical activity.

No racial differences in gonadal and adrenal steroids were observed, and steroid hormone concentration did not correlate with bone density of either the radius or the spine, suggesting that the racial differences in bone density observed in this study are not attributable to racial differences in either adrenal or follicular phase gonadal hormone concentration.

These findings to date support the initial hypotheses and demonstrate, for the first time, striking evidence of racial differences in bone homeostasis and calcium metabolism in pre- and post-menopausal women. In addition, the observation of significant premenopausal bone loss in both racial groups has important implications for the initiation of new research and preventive trials which should focus on intervention during childhood, adolescence, and early adulthood.

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Public Policy and Geriatrics:

The International Leadership Center on Longevity and Society of the Department of Geriatrics and Adult Development at Mount Sinai Medical Center

Malvin Schechter, M.S.

Many major policy issues for contemporary America and other nations arise from the demographics of population aging. The increase in absolute and relative numbers of people over age 65 influences society in many ways, with ramifications in health care, economics, housing, transportation, nutrition, and politics. For all professionals in health care, an understanding of population aging and its institutional ramifications appear essential to effective practice appropriate to all stages of the longer average span of life.

For this reason, the Department of Geriatrics and Adult Development at Mount Sinai Medical Center has established a policy center to collect, analyze, and interpret information and trends for health-care professionals and for the makers of public policy. The policy center also serves as a vehicle for teaching health-care trainees and for the generation of new information needed to guide policy development.

This center—the International Leadership Center on Longevity and Society (U.S.), or ILCLS—takes the view that the older population of our country, about 33 million persons, or one in seven Americans, is a resource for the center itself and for society. Contrary to myth, this population is mostly well and able. Some older people, chiefly among the two million persons aged 80 and older, need support from health and social and other services in order to survive and function at a reasonable level of satisfaction with life. The center's primary foci are on policy issues affecting geriatrics and productive aging.

Preserving or developing the conditions under which late life may be productive and secure with and without infirmity is a social, family, and personal responsibility. Unfortunately, policies to promote goals of productive and secure aging are obstructed by prejudice against older people, or ageism, and by gaps in information. Often, the negative image older people have had of themselves and the negative image others have held of older people has restricted the contributions they could make to society, community, family, and self. Ageism—recognized as a force in political, economic, and health affairs—is a professional as well as a general issue.

The center was intended from the beginning to serve internal as well as external purposes, that is, to serve as an educational vehicle for faculty and trainees of the department on public and private sector trends affecting geriatrics, and to present our data, analyses, and interpretations to professional and lay audiences. The goals of the center are to:

- Identify the salient problems and opportunities presented by population aging and increased life expectancies in the United States and elsewhere
- Promote biomedical and socioeconomic research on longevity issues, including productivity, health maintenance, health and social services, quality of life, and social roles
- Stimulate the development of informed policymaking related to longevity through collaboration among researchers and policymakers in the public and private sectors
- Disseminate information to the general public, lay and professional leaders, and the Mount Sinai community of health-care professionals

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From the Department of Geriatrics and Adult Development and the International Leadership Center on Longevity and Society (U.S.), The Mount Sinai Medical Center, New York, NY. Address reprint requests to Malvin Schechter, Associate Director of the International Leadership Center, Box 1070, The Mount Sinai Medical Center, New York, NY 10029.

Educational Support Functions

Efforts are made to inform medical students, fellows, and practicing physicians about the public and private programs that pay for and otherwise influence the delivery of services to older people. The syllabus for the mandatory rotation of fourth-year medical students through the department contains introductory material on the demography and socioeconomics of older Americans (including utilization of health and social services), and on the rationale, history, politics, and operations of Medicare, Medicaid, and private insurance (including how physicians and hospitals are paid).

In the center's view, the professional and financial environments for geriatrics have to change if geriatrics is to thrive and influence mainstream medicine. For example, Medicare was designed to extend to retirees the kind of health insurance benefits purchased through employment for working people. This approach excluded or skimped on long-term or "custodial" care, preventive services, outpatient drugs, and mental health services. Physicians were generously rewarded for procedures associated with acute care but not at all adequately for time spent in studies of the medical status of frail patients. Payment arrangements did not extend beyond the physician to cover the multidisciplinary geriatrics team (including nurse, social worker, and others). Consequently, the curious result of an insurance program designed specifically for older people was the only weak support to geriatrics.

In 1986, the department held a federally supported policy conference at Mount Sinai, "Paying Physicians for Geriatric Care." The conference utilized a study conducted among experts in geriatrics and among rank-and-file practitioners (1, 1A). These studies and the conference, which were funded in part by the National Center for Health Services Research and Health Care Technology, were precursors of the center's growing interest in health economics as a basis for policy development.

When the U.S. Congress created the Physician Payment Review Commission in 1986 to provide advice on Medicare policy, Robert N. Butler, the department chairman, was appointed to a two-year term and gave the commission a focus on geriatrics issues, using data gathered by the department at Mount Sinai. The commission recognized that physicians systematically received less payment for evaluation and management services in relation to physician time and effort than for invasive and imaging procedures (2). Although the commission promoted the development of a resource-based relative value scale for Medicare, there were shortcomings for geriatrics in the initial approach (for example: case vignettes for analyzing resource inputs did not include old or very old patients).

In the area of long-term care, the center's activities include papers, editorials, a conference, and a book. In 1983, a conference, "Long-term Care Insurance: If Not Now, When?" was held at Mount Sinai. A paper on health and long-term care as an issue important to women was presented in 1986 to a meeting sponsored by Resources for Midlife and Older Women, Inc., and the American Association of Retired Persons (3). In 1987, the center produced articles for two major medical publications (4, 4A) and a lecture for New York State policymakers (5).

Among other publications, the center furnished a section on health insurance for the first edition (1990) and the second edition (in press) of The Merck Manual of Geriatrics (6). The Twentieth Century Fund commissioned a study, soon to be published, on the organization and financing of a geriatrics-based expansion of Medicare as part of the general reform of American health care (7). Informal presentations were made by Robert Butler to the Pepper commission (U.S. Bipartisan Commission on Comprehensive Health Care) in Washington in 1989 on the design of a public long-term care strategy and the need for public support of geriatrics-related research.

On the theme of productive aging, the center has developed a newsletter called *Productive Aging News* which it has been publishing since 1986, experimented with seminars for human resources executives, and held preretirement sessions for employee groups, focusing on health promotion and disease prevention.

Role of the Center in International Collaboration

The center has sponsored two international conferences that eventuated in books (8, 8A). Because of Japanese interest in the issues of productive aging and long-term care, the center in 1990 assisted in the creation of a counterpart in Tokyo. Funded by business organizations, the Tokyo center is directed by Hideo Ibe, Ph.D., a leader in social welfare policy. The Tokyo center republishes *Productive Aging News* in Japanese and sponsors its own magazine on productive aging; the U.S. center has in turn published a digest in English of Japan's 10-year plan to promote health and social services for the aged (9) and has also stimulated a report on older people living alone in Japan (10). This report is a counterpart to studies by the Commonwealth Fund Commission on elderly people living alone, which was chaired by Robert Butler during its five-year existence in 1985–1990.

The center is preparing a comprehensive background paper on optimal environments for older persons. The paper is to be the basis of discussions at a Tokyo symposium to be sponsored by the Sasakawa Health Science Foundation in 1994 (11).

With advice from its Projects Advisory Group, representing academic, business, and other interests, the center has adopted a work plan with these international features:

- Completion of the *Almanac on Longevity and Society: Japan and the United States Compared*, by Charlotte Muller of ILC (U.S.) aided by In Huh, with the cooperation of ILC (Japan)
- Development of an international scholarly exchange program
- Initiation of an international program in comparative health economics
- Development of a network of contacts in policy and technical affairs in the United States and abroad

Although the center has been known internationally only a short time, it has received a wide range of visitors. As a quid pro quo for providing visitors with information on policies and programs relevant to productive aging and comprehensive care of the elderly, the center routinely and systematically solicits similar information from its visitors and recruits them into its network of contacts. An interview guide has been designed for this purpose.

The Role of the Center Domestically

The center was a cosponsor in May 1993 of a meeting of leading scientists on strategies to delay the onset of dysfunctions of later life. This was the first of a series of conferences to which business as well as science leaders are invited in an effort to foster collaboration in scientific development.

Another effort to promote collaboration was a series of center-organized seminars for invited scholars within the Graduate Center, City University of New York on productive aging and long-term care. The seminars drew specialists in such diverse areas as political science, psychology, economics, history, housing and environmental studies, and anthropology.

The center has also developed collaborative relationships through its Projects Advisory Group, the Alliance for Aging Research (Washington), the Third Age Center at Fordham University (New York), the University of Michigan, the Maxwell School of Citizenship and Public Affairs of Syracuse University, and the University of California (San Francisco).

The center arranged a summer program to orient long-term-care policy interns of the National Academy of Social Insurance in Washington, D.C. The center also is host to science writers of the Columbia University Graduate School of Journalism. In further association with that school, the center is developing a program to orient journalists on scientific and social policy issues of population aging.

In preparation is a book on the impact of longevity on society, dealing with health care, pensions, and family life. In addition to a factual presentation of major intersecting social trends affecting individuals and families, the book will offer proposals on individual and societal adjustments to improve the quality of life for old and young, including health and economic security.

Conclusions

Even before the inception of the medical school 30 years ago, Mount Sinai Medical Center manifested broad interests beyond clinical medicine in social and public policy issues. The first dean of the medical school, George James, M.D., who was also president of the medical center, had served as New York City Health Commissioner and was a leading commentator on questions of America's adaptation to an older population, chronic disease and disability, and public health. He testified before Congress frequently, notably on issues related to medical education and the inception of Medicare. The current president of the medical center, John W. Rowe, M.D., a geriatrician, carries on that tradition, as does Robert Butler, who was the founding director of the National Institute on Aging.

The policy center expresses longstanding interests of the Mount Sinai community. As part of the basic plan of the Department of Geriatrics and Adult Development, the development of a policy center was welcomed in 1982 by the Board of Trustees and Thomas Chalmers, M.D., then president and dean. Despite difficult times for fund-raising in the recent past, Mount Sinai itself has augmented private grants made specifically to the center.

Because of its milieu in a department and medical center that daily encounters older people and their families as well as problems in the delivery of services, the policy center is hardly an ivory tower activity. It has begun to make distinctive contributions at the institutional, national, and international levels to the definition and analysis of longevity issues.

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11	**Evening Seminar: What's New for Cancer Patients?** Holiday Inn Crowne Plaza Ezra M. Greenspan, MD Mary-Ellen Siegel, MSW
12–13	**Eastern Group Psychotherapy Society Annual Conference** Robert Friedman, PhD Hillel Swiller, MD
12—14	**Soc for Clinical and Experimental Hypnosis: Introductory Clinical Hypnosis Workshop** Marianne S. Andersen, PhD Stephen Snyder, MD
17	**The Dean's Lecture Series, 4 PM Hatch Aud** **Manipulating the Mouse Embryo: From Cells to Genes** Janet Rossant, PhD, Mt Sinai Hosp of Toronto

DECEMBER 1993

7	**Training in Child Abuse Recognition & Reporting** 6 PM Hatch Aud Katherine Teets Grimm, MD **repeated 2/1, 3/29, 6/28**
8	**The Dean's Lecture Series, 4 PM Hatch Aud** **Using an Ancient Enzyme to Regulate the Fate of RNA: How Eukaryotes Sense and Control a Toxic Nutrient** Richard D. Klausner, MD, Natl Institutes of Health
8–11	**Myofascial Pain: Diagnosis & Treatment** Andrew A. Fischer, MD

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(to be announced)	**Symposium on Women's Health Care Issues in the 90's: For Primary Care Providers** Michael Brodman, MD Martin E. Goldman, MD Stacey E. Rosen, MD
12	**The Dean's Lectures Series, 4 PM Hatch Aud** **Memory and the Mind** Patricia Goldman-Rakic, PhD Yale University School of Medicine
14	**Brachytherapy for Prostate Cancer** Nelson N. Stone, MD
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22	**American Academy of Psychiatry and the Law Conference** Karl M. Easton, MD
23–27	**International Trauma Anesthesia & Critical Care Soc: 1994 Trauma Anesthesia Update** Lake Tahoe, California Kenneth J. Abrams, MD
24–28	**40th Comprehensive Sinus Surgery Course** William Lawson, MD, DDS Hugh F. Biller, MD
29–30	**Soc for Clinical & Experimental Hypnosis: Advanced Clinical Hypnosis Workshop** Marianne S. Andersen, PhD Stephen Snyder, MD

FEBRUARY 1994

2–6	**Geriatrics Board Review Course** Robert N. Butler, MD, Judith Ahronheim, MD, Gabriel Gold, MD
5–6	**Advanced Hypnosis in Behavioral Medicine, Psychosomatic Disorders & Consultation Liaiso Psychiatry** Harold J. Wain, PhD, Steven Snyder, MD
9	**The Dean's Lecture Series, 4 PM Hatch Aud** **Molecular Properties of Voltage Gated Ion Channels** William A. Catterall, PhD Univ of Washington School of Medicine

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4	**Issues in Medical Ethics 1994: Scientific Medici Alternative Care, and Third-Party Payers** Rosamond Rhodes, PhD
9	**The Dean's Lecture Series, 4 PM Hatch Aud** **Mechanism & Regulation of Protein Transport Early in the Secretory Pathway** Randy Schekman, PhD University of California at Berkeley
5–12	**Skull Base Surgery** Chandranath Sen, MD & Peter Catalano, MD
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18	**25th Annual Communications Disorders Conference** Arnold Shapiro

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7–8	**Alternate Treatments for Localized Carcinoma of the Prostate: Radical Perineal Prostatectomy Brachytherapy, Cryosurgery** Nelson N. Stone, MD
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20–22	**Aortic Surgery Symposium IV** New York Hilton & Towers Randall B. Griepp, MD
22–23	**Thyroid Disease and the Eye** Arthur L. Millman, MD

MAY 1994

7	**Conference on Mediastinal Diseases** Steven M. Keller, MD Paul A. Kirschner, MD
8	**Echocardiography Workshop** Martin E. Goldman, MD
9–13	**Consultant's Course in Cardiology** Louis E. Teichholz, MD Richard Gorlin, MD Simon Dack, MD
11	**The Dean's Lecture Series, 4 PM Hatch Aud** **Signal Transduction by Receptors that Regulate Tyrosine Phosphorylation** Joseph Schlessinger, PhD NYU School of Medicine

JUNE 1994

8	**The Dean's Lecture Series, 4 PM Hatch Aud** **Receptor Protein-tyrosine Kinases and Phosphatases and Their Substrates** Tony Hunter, PhD The Salk Institute For Biological Studies

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